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Vol. 26 SEPTEMBER, 1949 No. 3

SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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Original Communications

Society of University Surgeons

The Rate of Conversion of Administered Inorganic Radioactive Iodine Into Protein-Bound Iodine of Plasma as an Aid in the Evaluation of Thyroid Function. Dwight E. Clark, M.D., Robert H. Moe, M.D., and Evelyn E. Adams, M.D., Chicago, Ill. ---------- 331

Potassium Deficiency in Surgical Patients. Henry T. Randall, M.D., David V. Habif, M.D., John S. Lockwood, M.D., and S. C. Werner, M.D., New York, N. Y. ---------- 341

Observations in Jejunal Alimentation. Clarke T. Case, M.D., Robert M. Zollinger, M.D., Charles H. McMullen, and John B. Brown, Ph.D., Columbus, Ohio ---- 364

The Influence of Caloric Intake Upon the Fate of Parenteral Nitrogen. Edwin H. Ellison, M.D., Robert S. McCleery, M.D., Robert M. Zollinger, M.D., and Clarke T. Case, M.D., Columbus, Ohio ---------- 374

Preschool Age Repair of Hypospadias With Free Inlay Skin Graft. Forrest Young, M.D., and John A. Benjamin, M.D., Rochester, N. Y. ---------- 384

A Method for Controlling Urinary Incontinence. Orvar Swenson, M.D., Harold F. Rheinlander, M.D., and Keith Merrill, Jr., M.D., Boston, Mass. ---------- 405

(Contents continued on inside back cover)

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SURGERY

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Vol. 26, No. 3, September, 1949. Surgery is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription price: United States, its possessions, Pan-American Countries, $10.00 a year; Canada and foreign, $11.00. Entered as Second-Class Matter January 20, 1937, at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Printed in U. S. A.

SURGERY

VOL. 26 SEPTEMBER, 1949 No. 3

Original Communications

Society of University Surgeons

THE RATE OF CONVERSION OF ADMINISTERED INORGANIC RADIOACTIVE IODINE INTO PROTEIN-BOUND IODINE OF PLASMA AS AN AID IN THE EVALUATION OF THYROID FUNCTION

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CHICAGO, ILL.

(From the Department of Surgery of the University of Chicago)

RADIOACTIVE iodine is being employed today by many investigators, not only in the treatment of diseases of the thyroid, but as a means of studying the function of the thyroid gland. Two methods—urinary excretion and uptake by the thyroid gland—have been used in following the fate of administered radioactive iodine in the various thyroid states. Extensive studies on the rate of excretion of radioactive iodine in cases of hyperthyroidism, euthyroidism, and hypothyroidism have been made by a number of investigators.[1-5] While this method has the advantage of simplicity, it requires the assumption that the iodine which is not excreted in the urine must be in the thyroid gland. Poor correlation was found by Quimby and McCune[6] between values for thyroid uptake as determined by direct measurement over the gland and those computed from urinary excretion. Hamilton and Soley,[4] Hertz, Roberts, and Salter[1] could not account for the total dose by combining the estimated content of the thyroid gland and the calculated amount excreted in the urine. Further disadvantages are in the wide range of excretion rate in the various thyroid states and the inaccuracy in urine collection. McArthur and associates[5] found that the mean urinary excretion in thyrotoxic patients was 25 per cent, range 7 to 45 per cent, and in euthyroids the average was 59 per cent, range 23 to 98 per cent. In the range of 20 to 40 per cent there was a considerable overlapping between the thyrotoxic and nonthyrotoxic individuals. In hypothyroid subjects the range of elimination was from 75 to 95 per cent. The discovery of a low excretion is an adjunct in establishing the diagnosis of thyrotoxicosis,

This work was aided in part by the Charles H. and Mary F. S. Worcester Memorial Fund, and by an institutional grant from the American Cancer Society.

Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 24-26, 1949.

The radioactive iodine used in this investigation was supplied by the Oak Ridge National Laboratories, Oak Ridge, Tenn., and obtained under allocation from the United States Atomic Energy Commission.

particularly in cases where the diagnosis is not clear. The finding of a high urinary excretion facilitates the exclusion of thyrotoxicosis in patients with hypermetabolism due to other diseases such as leucemia, lymphoma, hypertension, and cardiac failure.

Measurement of the uptake permits a study of the rate and extent of the concentration of radioiodine in the gland. Werner, Quimby, and Schmidt[7, 8] have made a very careful study of the uptake in various thyroid conditions. They based their results on the per cent uptake of a tracer dose in twenty-four hours. The normal range of uptake was between 10 per cent and 35 to 40 per cent. An uptake in excess of 50 per cent was held to be specific for thyroid overactivity. There was a slight overlap of uptake between the euthyroid and hyperthyroid patients. Stanley and Astwood[9] have used the rate of accumulation during a given period as an index of thyroid function. By plotting the number of counts per second against the square root of the time in minutes a straight line of uptake is revealed in the first four to six hours and the slope of this line is calculated. They have termed the slope of the line as the accumulation gradient. This method may narrow the percentage overlap between the normal and thyrotoxic patients, but to date it has been applied only to the evaluation of the effectiveness of the antithyroid drugs.

The level of protein-bound iodine in the plasma as determined chemically seems to be a good indicator of thyroid activity and correlates well with the basal metabolic rate and the clinical findings.[14, 15] The methods are rather complicated, expensive, and time consuming. Erroneous values due to contamination may occasionally occur.

Chaikoff, Taurog, and Reinhardt[10] found that the rate of incorporation of injected radioactive iodine into the protein-bound iodine fraction of plasma is depressed in thyroidectomized rats and increased in rats and guinea pigs injected with thyrotropic hormone and suggested that the rate of conversion may be a useful guide to thyroid activity.

The present investigation was undertaken to determine whether the rate of conversion of orally administered inorganic radioactive iodine into protein-bound iodine of the plasma would be a useful guide clinically in determining thyroid activity, particularly in borderline cases of hyperthyroidism and hypothyroidism.

PROCEDURE

Radioactive inorganic iodine (I^{131}) containing no carrier was administered by mouth to patients with varying degrees of thyroid function. Patients who were thought to have a normal or a low thyroid activity received 0.5 to 1.5 millicuries.* Individuals who had an elevated basal metabolic rate and were clinically classical hyperthyroid patients were given either a large tracer dose or a therapeutic amount of radioactive iodine. This latter dose varied from 3 to 8 millicuries,* depending upon the estimated size of the gland. None of the patients was fasted or on a special diet. Many of the cases were studied in the outpatient department.

*Oak Ridge standard.

Blood for determining the total amount of radioactive iodine in a given amount of plasma, and the per cent of this which was protein-bound, was drawn in exactly twenty-four hours. The blood (15 c.c.) was placed in a tube containing 5 drops of heparin. The plasma was separated by centrifugation. The total plasma I^{131} was determined by pipetting 1 c.c. of plasma into a small porcelain capsule, adding 1 c.c. of a diluting medium (.02 M NaOH; .0015 M KI; .005 M $NaHSO_3$) and 1 drop of silver nitrate solution (1 mg. $AgNO_3$ per milliliter). The capsule was gently shaken and dried by means of an infrared lamp within a closed hood. Care was taken to insure that the dried residue was uniformly distributed over the bottom of the capsule. The radioactivity was determined by means of a Geiger-Mueller counter. The method for determining the protein-bound I^{131} was similar to that used by Chaikoff, Taurog, and Reinhardt.[10] Plasma proteins were precipitated by adding 4 c.c. of 10 per cent trichloroacetic acid to 1 c.c. of plasma. The precipitate was separated by centrifugation and washed twice, each time with 4 c.c. of 10 per cent trichloroacetic acid. The precipitate was dissolved with 7 drops of 2 N NaOH in 2 c.c. of distilled water and transferred to a porcelain capsule. The tube was washed twice with small amounts of distilled water. One drop of silver nitrate solution (1 mg. $AgNO_3$ per milliliter) was added to the capsule. Radioactivity was determined after drying under an infrared lamp. Self-absorption was found to be negligible when 1 c.c. of plasma and small amounts of sodium hydroxide were used.

The results were expressed as the ratio of radioactivity in counts per second in the protein fraction to the total plasma radioactivity in counts per second. We have designated this as the conversion ratio.

$$\text{(Conversion ratio} = \frac{\text{Protein-bound } I^{131} \text{ in c/s} \times 100)}{\text{Total plasma } I^{131} \text{ in c/s}}$$

The conversion ratio was determined as soon as possible after the basal metabolism test had been obtained. Each of the cases received individual evaluation and was classified on the basis of the final clinical diagnosis. A careful history was obtained in reference to previous medication, when medication was discontinued, and if any recent laboratory procedure, which involved the use of an iodized solution, had been performed.

RESULTS

Patients With Hyperthyroidism.—Twenty-eight patients in whom the ultimate diagnosis was hyperthyroidism were included in this group (Table I). Every patient has responded to some form of treatment or presented a classical picture of uncomplicated primary thyrotoxicosis and is responding to therapy. The conversion ratio ranged from 45 to 96 per cent with an average of 78.5 per cent (Fig. 1). Only one patient showed a turnover under 50 per cent. This patient (Case 1, S. P.) had discontinued propylthiouracil only two weeks prior to the test and had very minimal signs of recurrence. From subsequent experience if four weeks had been allowed to elapse before determining the conversion ratio this patient would have probably had a ratio above 50 per cent.

There seemed to be a relative correlation between the severity of the hyperthyroidism and the conversion ratio. Those cases where the rate of

TABLE I. CONVERSION RATIO IN HYPERTHYROIDISM

NO.	PATIENT	AGE (YR.)	SEX	TYPE OF GLAND	B.M.R.	CONVERSION RATIO (IN %)	REMARKS
1	S.P.	50	M	Dif.	+17	45	Off propylthiouracil for 2 weeks prior to I^{131} therapy; previous thyroidectomy; diabetes; responded to I^{131} treatment
2	E.R.	58	F	Dif.	+21	53	Taking propylthiouracil 50 mg. every other day, discontinued 1 week before I^{131} therapy; previous thyroidectomy; responded to I^{131} treatment
3	M.K.	58	F	Dif.	+25	59	Osteoporosis; previous thyroidectomy; responded to I^{131} treatment
4	H.W.	33	F	Nod.	+23	61	Two previous thyroidectomies; off propylthiouracil for 6 weeks; responded to I^{131} treatment
5	J.R.	25	M	Dif.	+19	65	Off propylthiouracil for 4 weeks; responded to I^{131} therapy
6	V.S.	26	F	Dif.	+39	68	Responded to propylthiouracil
7	B.S.	42	F	Nod.	+42	71	Two previous thyroidectomies, no recent antithyroid drugs; responded to I^{131} treatment
8	S.B.	35	M	Dif.	+35	74	No previous medication; responded to I^{131}
9	A.S.	52	F	Dif.	+42	75	No previous medication; responded to propylthiouracil
10	E.D.	45	F	Dif.	+45	76	Off propylthiouracil for 2 months; responded to I^{131} treatment
11	M.L.	58	F	Dif.	+15	77	Off propylthiouracil for 6 weeks; responded to I^{131} therapy
12	R.E.	76	M	Nod.	+45	78	Parkinsonism; responded to propylthiouracil
13	E.F.	58	F	Nod.	+26	78.9	Discontinued propylthiouracil for 1 month; responding to I^{131} treatment
14	N.M.	32	F	Dif.	+39	79	Responded to propylthiouracil
15	R.H.	33	F	Dif.	+42	80	Stopped thiouracil for 2 weeks; responding to I^{131}, classical hyperthyroid
16	J.R.	70	M	Dif.	+ 8	81	Responded to propylthiouracil; subsequently treated with I^{131}; cardiac
17	S.W.	52	F	Dif.	+39	81	No previous medication; cardiac; treated with I^{131}, classical hyperthyroid
18	P.F.	28	F	Dif.	+30	82	Off iodine therapy for 1 week; treated with propylthiouracil and thyroidectomy
19	A.T.	47	M	Dif.	+32	85	Lugols for 3 days before I^{131} therapy; classical thyrotoxicosis
20	L.M.	56	F	Dif.	+43	85	Hypertension; stopped propylthiouracil for 3 weeks; responded to I^{131} therapy
21	A.D.	62	F	Nod.	+31	87.5	Stopped Lugols solution 2 weeks before; responded to I^{131} therapy
22	F.S.	44	M	Dif.	+59	90	No previous medication; responded to I^{131} therapy
23	M.B.	69	F	Nod.	+49	91.5	No previous medication; treated with I^{131}; classical thyrotoxicosis
24	T.M.	51	F	Dif.	+28	91.8	No previous medication; responded to I^{131} therapy
25	J.H.	31	F	Dif.	+32	95	No previous medication; treated with propylthiouracil and thyroidectomy
26	M.K.	65	F	Dif.	+30	95	Responded to I^{131} treatment
27	F.S.	45	F	Nod.	+64	96	Previous thyroidectomy; classical hyperthyroid, responding to I^{131} treatment
28	R.C.	30	F	Dif.	+72	96	Off antithyroid drugs for 1 month; treated with I^{131}, classical hyperthyroid

incorporation fell between 50 and 70 per cent had only mild signs and symptoms of thyrotoxicosis while the more toxic cases converted over 70 per cent. Every patient that clinically presented a picture of marked thyroid activity had a ratio of 90 per cent or over.

There was no overlapping between the upper limit of normal and the hyperthyroid patients. At the present time all patients with a conversion ratio of 50 per cent or higher are considered as having hyperthyroidism.

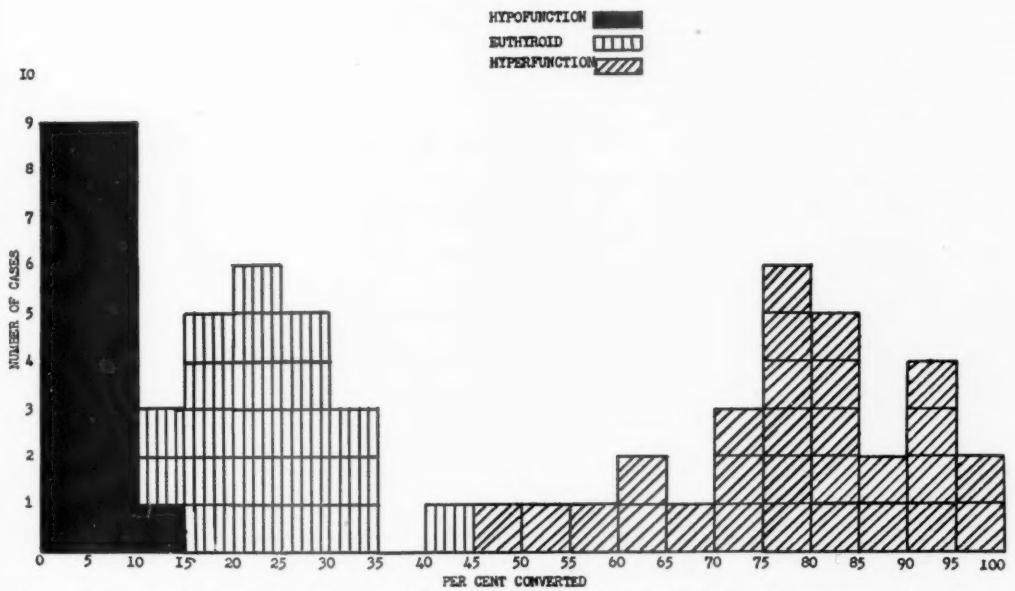

Fig. 1.—Distribution of conversion ratios in hyperthyroid, euthyroid, and hypothyroid patients. (Based on ultimate clinical diagnosis.)

Case 16 (J. R.) is of particular interest and deserves special consideration. He was an elderly man who had been treated several years for heart disease. He exhibited very few signs of hyperthyroidism and the basal metabolic rate was +9. Radioiodine studies were done and the conversion ratio was 81 per cent. He was placed on propylthiouracil and the cardiac condition improved, he felt much better, and gained twenty-two pounds of weight. When the propylthiouracil was discontinued he began to lose weight and the cardiac condition became worse. On the basis of this response this man was considered as being a masked hyperthyroid and was treated with radioactive iodine.

Patients With Euthyroidism.—Twenty-two patients were studied who on the basis of clinical observation and the basal metabolic rate were thought to have an essentially normal thyroid activity (Table II). Sixteen of the group had diseases unrelated to the thyroid, three had benign adenomas, two had carcinomas of the thyroid which were treated by partial thyroidectomy and one had severe malignant exophthalmos. The latter (Case 15, M. J.) had repeated normal basal metabolic rates and showed no manifestations of hyperthyroidism. None of the numerous observers who saw this patient felt that she had thyrotoxicosis.

TABLE II. CONVERSION RATIO IN EUTHYROIDISM

NO.	NAME	AGE (YR.)	SEX	DIAGNOSIS	B.M.R.	CONVERSION RATIO (IN %)
1	O.A.	45	F	Carcinoma of cervix	+ 3	21
2	E.H.	28	F	Incisional hernia	+12	29
3	H.H.	44	M	Melanosarcoma	–	15
4	J.H.	40	M	Fetal adenoma of thyroid, chronic duodenal ulcer	– 7	32
5	B.G.	44	F	Hemorrhoids, anxiety symptoms	+15	24
6	B.G.	30	F	Carcinoma of thyroid, subtotal thyroidectomy	+10	16.6
7	E.L.	33	F	Uterine fibroids, transection of cord at L-2	–	30
8	S.R.	7	F	Carcinoma of thyroid	–10	21
9	L.S.	29	F	Intestinal obstruction	–	28.2
10	E.S.	23	M	Gastric ulcer	– 1	42
11	M.S.	57	F	Carcinoma of pancreas	–	33.7
12	M.C.	74	F	Biliary fistula	–14	21
13	F.D.	39	F	Carcinoma of breast, previous subtotal thyroidectomy	–16	23.8
14	C.E.	22	F	Ulcerative colitis	+12	35
15	M.J.	39	F	Malignant exophthalmos, no signs of thyrotoxicosis	– 1	24
16	G.S.	26	M	No organic disease	–23	26
17	M.T.	35	F	Adenoma of thyroid	– 2	17
18	A.T.	39	F	Functional bowel distress	+12	17
19	F.T.	51	F	Cyst of kidney	+ 3	18.5
20	J.V.	59	M	Inguinal hernia	–	27.3
21	E.T.	27	F	Appendicitis	–13	13
22	E.K.	61	F	Adenoma of thyroid	–11	13.3

The range of the conversion ratio was 13 to 42 per cent with an average of 24 per cent (Fig. 1).

Patients With Hypothyroidism.—The expected low conversion ratio in hypothyroidism or myxedema was confirmed in 19 cases (Table III). The range was from 2.7 to 12.5 per cent, with an average of 6 per cent. All of the cases in this group except one converted less than 10 per cent (Fig. 1). Five of the patients were receiving thyroid extract which maintained their basal metabolic rate at a normal level. We have considered all patients who convert less than 10 per cent to have an abnormally low thyroid activity.

Werner, Quimby, and Schmidt[8] found a very low uptake of radioiodine in six cases of acute thyroiditis despite a normal basal metabolic rate. In the one case which we studied these findings were confirmed. The patient had a basal metabolic rate of +6, low uptake over the thyroid, converted only 6.4 per cent, and excreted 85 per cent in seventy-two hours.

Patients With Cardiac Disease and Hypertension.—Seven patients who had hypertensive cardiovascular disease with an elevated basal metabolic rate and two with essential hypertension without apparent cardiac disease but an elevated basal metabolic rate were studied (Table IV). In all the cases where there was marked cardiovascular disease the conversion ratio was under 10 per cent, placing them in the hypothyroid range. This would suggest that the body has suppressed the action of the thyroid in order to decrease the metabolic activity and thus reduce the work of the heart. The essential hypertensive patients converted 36 and 23.8 per cent, which would place them in the euthyroid group.

TABLE III. CONVERSION RATIO IN HYPOTHYROIDISM

NO.	PATIENT	AGE (YR.)	SEX	DIAGNOSIS	B.M.R.	CONVERSION RATIO (IN %)
1	R.B.	23	M	Thyroid carcinoma, total thyroidectomy, myxedema	−25	3.5
2	E.B.	63	F	Myxedema	−40	5.0
3	F.L.	24	M	Carcinoma of thyroid, myxedema	−40	5.0
4	K.D.*	65	F	Carcinoma of thyroid	− 6	2.7
5	M.O.	54	F	Carcinoma of thyroid, myxedema	−35	12.5
6	R.P.*	11	M	Carcinoma of thyroid	−13	7.0
7	C.S.*	52	M	Carcinoma of thyroid, myxedema	−13	4
8	P.S.	62	M	Hürthle cell carcinoma, myxedema	−38	6.1
9	L.S.*	44	F	Carcinoma of thyroid	− 4	5.0
10	M.N.	52	F	Carcinoma of thyroid	−20	7.1
11	A.S.	55	F	Myxedema	−30	3.0
12	J.K.	41	F	Hypothyroidism, pernicious anemia	−21	7.0
13	M.B.	39	F	Myxedema	−23	7.0
14	J.G.*	9	M	Congenital hypothyroidism	− 9	6.8
15	C.O.	44	M	Myxedema	−37	7
16	M.T.	56	F	Post-thyroidectomy, hypothyroidism	−30	3.3
17	F.W.	17	M	Craniopharyngioma	−39	8.8
18	E.H.	44	F	Hypothyroidism, anxiety state	−19	4
19	O.P.	59	M	Myxedema, mild	−18	9

*Patient receiving thyroid extract.

TABLE IV. CONVERSION RATIO IN CARDIAC AND HYPERTENSIVE STATES*

NO.	NAME	AGE (YR.)	SEX	DIAGNOSIS	B.M.R.	CONVERSION RATIO (IN %)
1	B.S.	67	F	Auricular fibrillation with myocardial defect, diabetes mellitus	+23	7
2	A.B.	58	M	Hypertensive cardiovascular disease, mild decompensation	+14	6.2
3	A.G.	67	F	Hypertensive cardiovascular disease with insufficiency, nodular goiter	+36	1.5
4	T.G.	50	M	Mild cardiac failure	+11	5
5	E.K.	58	M	Hypertensive cardiovascular disease, diabetes mellitus	+24	8.4
6	I.M.	73	F	Hypertensive cardiovascular disease	+28	8
7	C.H.	51	F	Hypertensive cardiovascular disease with moderate decompensation	+31	6.4
8	R.L.	39	M	Essential hypertension, had sympathectomy	+31	36
9	E.C.	57	M	Essential hypertension, no apparent cardiac disease	+22	23.8

*Not included in Fig. 1.

DISCUSSION

The chemical nature of protein-bound iodine is not yet fully understood, but it is generally accepted that its level in the plasma is a good index of circulating thyroid hormone. Bassett, Coons, and Salter[11] found that about 30 per cent of the protein-bound iodine is in a diiodotyrosine-like fraction, while the remainder is comprised of a thyroxine-like fraction. In myxedema, the thyroxine fraction practically disappears. In patients with normal or hyperactive thyroid function the increase in the protein-bound iodine is due chiefly to the thyroxine-like moiety. Morton, Perlman, and Chaikoff[12] administered tracer doses of radioiodine to normal guinea pigs and those treated for four days with thyrotropic hormone, and studied the rate of incorporation of the labeled iodine into radiodiiodotyrosine and radiothyroxine at two and twenty-six hours. By this method they showed that not only is the increase in the protein-bound iodine in the hyperactive group due mainly to thyroxine, but the rate of its elaboration is considerably increased over the control group.

No attempt was made in this study to fractionate the protein-bound iodine in the various thyroid states, but the greater conversion ratios in the euthyroid and hyperthyroid groups are presumably due to the increased production and elaboration of thyroglobulin. The data suggest that the rate of incorporation of radioiodine into newly formed protein-bound iodine can be determined with sufficient accuracy to be of value in determining thyroid activity.

In such studies the possibility of an "exchange" reaction occurring as a purely physicochemical phenomena presents itself. If such a reaction occurred in this study, we believe it is negligible or the amount of radioiodine in the protein precipitate would be higher in patients with hypothyroidism, particularly those receiving thyroid extract. By in vitro tests of adding radioiodine to plasma we were unable to detect any appreciable iodination of protein.

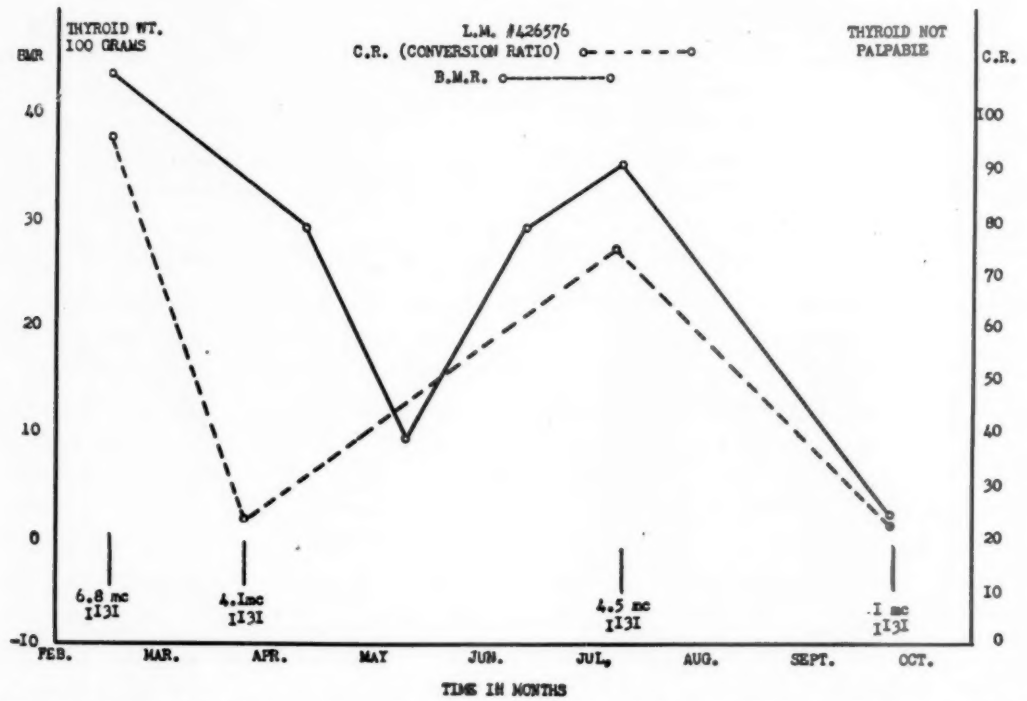

Fig. 2.—Correlation between changes in conversion ratio and basal metabolic rate in a case of hyperthyroidism treated with radioactive iodine.

The change in the conversion ratio in relation to the basal metabolic rate in cases of true hyperthyroidism seems to be similar to that found by the chemical determination of protein-bound iodine when elaboration of the thyroid hormone is blocked by antithyroid drugs. Fig. 2 shows the correlation between the conversion ratio and the basal metabolic rate in a case of hyperthyroidism treated with I^{131}. Five weeks after the initial dose of radioiodine the activity of the gland was changed so that the conversion ratio was normal, but the basal metabolic rate was still quite high. Six weeks later the basal metabolic rate had fallen to almost normal. The amount of radioactive iodine given was not sufficient to effect a cure and the patient had a recurrence of the symptoms. The basal metabolic rate increased as did the conversion ratio. At the

time of the administration of the third dose of radioactive iodine the basal metabolic rate was lower than at the beginning of the treatment and the clinical manifestations were less severe. The conversion ratio was lower and correlated well with the other findings. The final dose of labeled iodine was given when the basal metabolic rate had again returned to normal, at which time the ratio was found to be in the euthyroid range.

There are many extra-thyroidal factors which may influence the conversion ratio so that it is important to evaluate each case individually. Except in a few instances we have allowed a period of four weeks to elapse from the time of discontinuing antithyroid drugs, thiocyanate, or cough syrups containing iodine before determining the conversion ratio. Recent cholecystograms, bronchograms, or pyelograms may also alter the rate of incorporation of tagged iodine into the protein-bound fraction.

The type of gland did not seem to make any appreciable difference in the conversion ratio although most of the cases in the hyperthyroid group were thought to have diffusely hyperplastic glands. In the patients studied age did not seem to affect the conversion ratio. In many of the cases presented the urinary excretion and the uptake by the thyroid gland were determined. There was a good correlation in most of the cases between the conversion ratio, uptake, and excretion.

Doses of 1 to 1.5 millicuries were used in order to obtain significant counts in 1 c.c. of plasma. Although these are larger tracer doses than generally used, no adverse reactions have been observed. In cases of hyperthyroidism most all of them will require more I^{131} before a therapeutic response is obtained. In euthyroids approximately 50 per cent of the dose is excreted and the amount taken up by the gland is much less than that required to cause hypothyroidism. Crile, McCullagh, and Glasser[13] have estimated that it requires 30 millicuries to cause hypothyroidism in a patient with a normally functioning gland. Since it is well known from radioautograph methods that the localization of I^{131} in the thyroid gland is not uniform, the chances of having a small area intensely radiated are probably as great if 100 microcuries or 500 microcuries are fixed in the gland. The possibility of carcinoma developing in such an area warrants consideration, but there is no evidence either clinically or experimentally to suggest that the incidence will be significantly altered.

Many more cases with various thyroid states are being studied. Although in the cases presented there was no overlapping between the euthyroid and hyperthyroid group, it is possible that some overlapping may be found as more cases are studied since this procedure only estimates the rate of elaboration of the thyroid hormone and does not measure the sensitivity of the tissues to thyroxine.

SUMMARY AND CONCLUSIONS

1. The rate of conversion of orally administered radioactive iodine into the protein-bound iodine of the plasma has been studied in patients with various thyroid states and in patients with hypertension and cardiac disease with an elevated basal metabolic rate.

2. In normal man the conversion ratio ranged from 13 to 42 per cent.

3. All patients in whom the conversion ratio is 50 per cent or greater are considered to have a hyperactivity of the thyroid gland.

4. There is no overlapping between the hyperthyroid group and the euthyroid group in the cases studied.

5. Patients who convert 10 per cent or less are considered to have hypothyroid activity.

6. All of the patients with severe cardiac disease but an elevated basal metabolic rate show a low conversion ratio.

7. Two patients with hypertension but no apparent cardiac disease have a conversion ratio in the normal range.

8. The results suggest that the rate of incorporation of radioactive iodine into protein-bound iodine of the plasma may be a useful guide to thyroid activity.

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POTASSIUM DEFICIENCY IN SURGICAL PATIENTS

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THE work of which this paper is a partial report began as an intensive study of fluid and electrolyte problems on the Surgical Service of the Presbyterian Hospital in June, 1947, at which time the completion of a flame photometer made possible rapid and reasonably numerous determinations of sodium and potassium concentrations in biologic media. The opening of the surgical metabolic unit in January, 1948, made possible the accurate balance study of fluid, electrolyte, and nitrogen exchanges in patients both pre- and postoperatively. Two parallel and dependent lines of study then evolved, the methodical study of patients in the metabolic unit according to plan, and the day-to-day evaluation of the electrolyte and fluid status of critically ill patients on the general ward service, with special effort being made to evaluate and correct electrolyte imbalance as found and to maintain major surgical cases in as close balance as possible postoperatively. This paper reports some of our experiences, with particular emphasis on potassium deficiences in surgical patients, their correction, and prevention.

REVIEW OF PERTINENT LITERATURE

Since potassium is the major cation in the body, exceeding sodium by a ratio of more than two to one, the role of this ion in physiology has been the subject of numerous studies over a period of many years. Benedict[1] in 1915 showed that in starvation potassium was lost in direct relation to loss of nitrogen with 2.87 mM of K being lost with each gram of nitrogen in days 2 to 11 inclusive. Similar results were obtained by Gamble[2] in 1923 with K loss slightly in excess of expectation based on nitrogen loss and tissue analysis. In 1933 Butler[3] reported large losses of potassium in the stools and urine of two infants with diarrhea, and noted that the potassium loss far exceeded that expected from nitrogen loss. Darrow[4] and Gamble[5] in reporting metabolic studies on children with congenital alkalosis and diarrhea noted, in addition to an excessive chloride loss in the stool, which was considered to be the most significant factor in electrolyte imbalance, a very large loss of potassium in stool and in urine particularly during phases of increasing dehydration. Darrow observed plasma K levels as low as 1.5 meq. per liter in the untreated state, and showed in a series of balance experiments with one patient that clinical dehydration and potassium debts could develop with little loss of total body water, sodium, and water shifting into the cells, leading to extracellular dehydration, with continuing potas-

This work was supported in large part by a grant from the Research Grants Division, National Institutes of Health, Bethesda, Md.

Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 24-26, 1949.

sium loss in urine and stools. He also demonstrated that a relative potassium deficit could appear during a period of markedly positive nitrogen balance, and that potassium deficits were increased in periods of positive sodium balance. Although no symptoms other than generalized weakness were shown with the dehydration and K loss, the administration of additional potassium as KCl by mouth to supplement that taken in food proved of distinct benefit to the child.

In a paper discussing retention of electrolyte following acute diarrhea with severe dehydration in infants, Darrow[6] demonstrated by metabolic studies that loss of K from cells may amount to as much as one quarter of the total body stores of K. Much of the extracellular dehydration in some cases appeared to be due to loss of sodium by shift of sodium and water into cells. The usual replacement of extracellular fluid with saline or saline-bicarbonate mixtures restored extracellular deficits but actually increased potassium loss since additional sodium entered the cells. Two of his patients were treated with parenteral KCl and showed retention of K, Na, and Cl with rapid improvement which was subsequently maintained with KCl by mouth. Govan and Darrow[7] then reported a series of patients treated for infantile diarrhea and dehydration with a mixture of sodium and potassium chlorides and sodium lactate in which the mortality was only 3 of 50 as contrasted to 17 of 50 treated with sodium chloride and sodium lactate alone.

In diabetic acidosis Atchley and associates[8] showed loss of intra- and extracellular electrolytes after insulin withdrawal, and retention of these ions during the recovery period. In acidosis the K loss averaged 90 meq. a day, with nitrogen loss of 8.2 Gm. Danowski[9] also demonstrated increased K loss and nitrogen loss in diabetic acidosis and noted that the serum K fell markedly in the recovery phase. Butler[10] in recent metabolic studies of diabetic coma confirmed large potassium losses and used solutions containing potassium in repair to avoid sharp reductions in plasma K concentrations.

A series of reports[11, 12, 13] of cases of potassium deficiency in the recovery period following diabetic acidosis have shown K levels of 1.9 to 2.5 meq. per liter in plasma, accompanied by muscular weakness, difficulties in swallowing, and interference with respiration, in one instance requiring a respirator, but with rapid recovery following parenteral and oral administration of potassium salts.

Dehydration was studied extensively by Elkinton and Winkler[14] and their associates. They showed in the dog that in severe water depletion large amounts of potassium are excreted in high concentration by the kidneys. Great resistance to plasma K changes were noted, and it was observed with dehydration in animals with ureters tied that there is no mobilization of intracellular potassium. They suggested that high plasma K levels seen in hemorrhage and intestinal obstruction are due to marked alteration in cell metabolism. In an earlier paper[15] it was observed that 20 to 38 per cent of extracellular water could be lost, while from 30 to 50 per cent of intracellular water was mobilized, and that K loss was much greater than could be explained simply by tissue catabolism. In late stages sodium and chloride and

the extracellular fluid tended to be maintained while potassium and intracellular water losses rose steadily until K excretion in the urine reached 500 meq. per liter. In human subjects early stages of the same phenomenon were observed. In the first forty-eight hours of water deprivation extracellular losses predominated, but later losses were predominantly intracellular, and again the potassium loss far exceeded that expected from catbolism alone. By the end of four days water deficits were proportional to the ratio of extracellular to intracellular water.[16]

Black, McCancre, and Young[17] in a similar experiment with volunteers who ate a dry diet showed that extracellular sodium concentration rose while large amounts of potassium were excreted in urine. They stated that the kidney will preferentially excrete potassium over sodium or urea under these circumstances. Winkler and associates[18] demonstrated that with water deprivation the ingestion of foods containing nitrogen or potassium increases the obligatory urine output and the rate of dehydration. Recent studies by Elkinton[19] showed that potassium losses are great in dehydration, and when extracellular sodium is high, as when water loss is disproportionately greater than electrolyte loss. Cell sodium tends to be high under these conditions, while it is low in oliguria and in nephrectomized animals. The cell potassium is not necessarily elevated when cell sodium is low, but is always low when cell sodium is high. Cell potassium rises only when an exogenous source of potassium is available.

Brown, Currens, and Marchand[20] reported potassium deficiency in three cases of nephritis, with plasma levels of 2.0, 2.1, and 2.5 meq. per liter, and marked muscular weakness, followed by rapid recovery on the administration of potassium salts. They described electrocardiographic changes characterized by depressed ST segments in all leads and low voltage T waves which returned to normal after potassium administration. Similar electrocardiographic changes were reported by Holler[11]; in this connection it is of interest that Darrow and Miller[21] observed necrosis of myocardial fibers and replacement with fibroblasts in rats with potassium deficiency induced by desoxycorticosterone treatment.

Plasma potassium deficits have been observed at the time of crises of familial periodic paralysis by Ferrebee, Gerity, Atchley, and Loeb,[22] who also observed a decrease in renal excretion during attacks. Plasma K rose and renal excretion increased on recovery. In Cushing's syndrome Willson, Power, and Kepler[23] have reported plasma K values of 2.2 meq. per liter together with a high HCO_3 and low Cl. This alkalosis was unresponsive to the administration of NH_4Cl but responded to the administration of either KCl or potassium citrate with retention of potassium, drop in HCO_3, and rise in chloride.

Alkalosis has been reported as being associated with potassium deficiency states, and perhaps causing them. Yannet and Darrow[24] reported wide variations in muscle K in relation to phosphate and nitrogen, and observed that muscle water varied directly with cell sodium and potassium and inversely with the concentration of extracellular electrolytes. Yannet,[25] in an acute

experiment in cats, noted a rise in cell sodium with intraperitoneal bicarbonate administration. Darrow[26] found in rats with pyloric obstruction which were given glucose and water that serum K rose while serum Na and Cl fell, as did cell sodium and chloride. On the other hand, animals on diets low in chloride, and low in sodium, potassium, and chloride, showed a rise in serum bicarbonate and fall in serum chloride accompanied by a rise in cell sodium and a fall in cell potassium. Serum potassiums were low in these animals. It was also noted that cell water tended to be increased as sodium replaced potassium milliequivalent for milliequivalent.

Darrow, Schwartz, Iannucci, and Coville[27] have shown that there appears to be a definite and predictable relationship between serum bicarbonate and cell potassium once renal adjustment has been reached. In alkalosis produced in rats by a variety of means, including low K intake and adrenal cortical hormone treatment, it was noted that the higher the serum bicarbonate, the lower the cell potassium and the higher the cell sodium. It was concluded that patients having a potassium deficit may be expected to develop an alkalosis when treated only with sodium chloride, and this alkalosis will be refractory to sodium chloride therapy if the potassium deficit persists. The experimental results to be reported in the present paper confirm these observations. Marked potassium deficit has been reported with adrenal cortical hormone administration by Kuhlmann, Ragan, Ferrebee, Atchley, and Loeb[28] and by Ferrebee, Parker, Carnes, Gerity, Atchley, and Loeb.[29] The first study reported plasma potassium values one-half of normal with the development of marked muscular weakness which was cured by KCl administration, and the second noted the replacement of muscle potassium by sodium in animals under treatment.

Intravenous fluids have been studied for their effect on electrolyte and water balance. Hastings and Eichelberger[30] noted little change in intracellular volume with infusions of physiologic levels of sodium, chloride, and bicarbonate, but an increase in intracellular volume when alkaline solutions were infused. Flock, Bollman, Mann, and Kendall[31] showed that glucose infusions resulted in drops of plasma K levels in dogs, as did infusions containing sodium ion, particularly when combined with lactate or bicarbonate anions. The work of Fenn[32] and others has suggested that potassium is involved in glycogen synthesis in the liver and that this may account for some of the plasma K withdrawal associated with glucose infusions. Stewart and Rourke,[33] however, demonstrated large potassium losses with massive infusions of saline as well as with glucose infusions, the potassium appearing in the urine.

In a more recent series of studies, Iob,[34] Berry, [35] and Cooper,[36] and their associates, in observing various aspects of the effect of infusions and operation on renal function and potassium balance have noted in normal subjects a high initial rate of both water and potassium excretion in the urine when infusions of either saline or glucose and water were given. The potassium excretion far exceeded 2.7 meq. per gram of nitrogen loss which Berry uses as catabolic expectation. After the first few hours the rate of excretion of potassium is

higher in patients immediately postherniorrhaphy than in the controls, and highest of all in a group of patients who underwent combined abdominoperineal resections. In all cases the potassium loss exceeded that expected by nitrogen output by a wide margin. It appears that controls receiving saline or 5 per cent dextrose in saline solution lost more potassium than those on glucose, although variability is great.

Ariel, Abels, Pack, and Rhoads[37] reported a hypochloremic state refractory to sodium chloride administration occurring in certain surgical patients maintained on parenteral fluids following surgery for gastrointestinal cancer. These patients showed low serum chlorides, high bicarbonate levels, and hypoproteinemia, often with edema and hemoconcentration. They had received an average of 15 to 18 Gm. of sodium chloride a day for several days before onset, and showed weakness, lethargy, anorexia, nausea, and a mild ileus. They responded somewhat to plasma infusions after saline solution was reduced or excluded and improved rapidly when they began to eat. It was concluded that low proteins were the cause of the syndrome. Ireneus[38] reported four patients with low chlorides and alkalosis, languor, drowsiness, distention, dehydration, and oliguria, and noted hypotension and a wet gray skin. These were a patient with burns, one with a pyloric obstruction, and two patients with T-tube drainages of the common duct who excreted large quantities of bile. Mudge and Vislocky[39] observed high intracellular sodium and low potassium in a patient who demonstrated a similar picture, and have reported similar low potassium values in the muscles of patients suffering from renal acidosis in chronic form.

The use of potassium salts in rehydration following infantile diarrhea and potassium depleted states in diabetic acidosis and chronic nephritis has been mentioned. It is now well recognized in surgery that limitation of the use of sodium salts postoperatively is imperative; the work of Coller[40, 41] showed that the use of isotonic sodium chloride solution resulted in marked sodium retention and very large potassium losses together with cellular dehydration, and that saline solution well below isotonic concentration was far better as a replacement fluid. Moyer[42] noted the persistence of high serum bicarbonate and low chloride in the face of sodium chloride infusions in cases in which large potassium deficits are known to occur, and suggested the use of potassium salts particularly when the onset is slow and accompanied by weakness, atonia, and hypotension. Similarly, Maddock in a review article[43] and Abbott[44] mentioned Darrow's work and suggested that potassium salts might prove useful clinically. Darrow[45] suggested that potassium deficits occur when output exceeds intake, with change in equilibrium as in alkalosis, during rapid storage of nitrogen, and under the action of adrenal cortical hormone. He predicted that many unexplained low chloride, low potassium, high bicarbonate plasma findings in various clinical conditions may prove to be potassium deficits.[27, 46]

METHODS

Details of the methods and techniques employed in the metabolism unit will be reported at a later date. Serum sodium and potassium determinations in

urine, stool, and drainages were done with a modification of the internal standard flame photometer introduced by Barnes, Richardson, Berry, Hood, and Chappell in 1946.[47, 48] This instrument has a reproducible accuracy of 1 per cent for both sodium and potassium, and has the advantage of requiring only 1 to 2 c.c. of specimen. Chloride ion determinations were done by the method of Schales and Schales.[49] Bicarbonate determination was done as CO_2 content by the method of Van Slyke.[50] Nitrogen determinations were made by the Kjeldahl technique. Bloods were taken, except in emergencies, in the early morning before the day's fluids or food were started. When HCO_3 was to be tested for, bloods were taken under oil and allowed to clot and then all determinations were done on the serum. Sodium and potassium determinations alone were done on plasma from blood collected with careful precautions to avoid hemolysis and were placed in a 5 c.c. hematocrit tube containing approximately 0.1 mg. sodium heparin. This was immediately centrifuged and the determinations were made on the plasma. Urines, Miller-Abbott tube, and other drainages were collected as twelve or twenty-four hour specimens in covered containers. In computing outputs of water and electrolytes, care was exercised that exact measurements were made, and that irrigating fluids (as in Miller-Abbott tubes) were included in intake, and irrigation returns included in output.

	Determinations	Patients	Meq/liter
Sodium	67	32	141.00 ± 2.63
*Potassium	71	35	4.26 ± .43
Chloride	56	20	104.47 ± 2.71
HCO_3	(content)		27.6 ± 2.0

*Three patients had consistent K values of 5.0 to 5.3 without renal or other pathology.

Fig. 1.—Normal plasma values for sodium, potassium, and chloride ion concentrations as determined on control subjects.

RESULTS

Normal Electrolyte Values.—Preliminary normal values were obtained from a number of miscellaneous preoperative patients from the metabolic service who had no demonstrable disease other than hernia, inactive chronic cholecystitis, or nontoxic nodular goiter. Fig. 1 gives the figures obtained. These correspond closely to accepted normal values, and the variation as expressed by the standard deviations is seen to be quite small. The standard deviation for the potassium value is somewhat larger because of three patients

who had consistently high values in the range of 5.0 to 5.3 meq. per liter in the absence of any demonstrable cause. In this work any plasma potassium value between 3.8 and 4.6 meq. per liter is considered to be within the normal range, accepting the fact that an occasional individual may show a higher value. We have encountered relatively few high levels in surgical patients and most of these were in chronic or acute renal failure, as described by other workers.[14, 51, 52, 53] Low plasma potassium values and their possible significance will be discussed later.

Potassium Values Under Controlled Metabolic Conditions.—Three groups of patients were then studied in the metabolism unit. Group I consisted of patients who were fed a calculated standardized diet for fourteen days until operation, and then maintained for the day of operation and four days postoperatively on parenteral fluids consisting of dextrose in saline solution, dextrose in water, and 10 per cent amino acids. They illustrate the amount of potassium lost in relatively minor procedures. Fig. 2 shows the average plasma potassium values together with the average daily potassium loss in two patients, C. G., with a bilateral inguinal herniorrhaphy, and E. W., with a

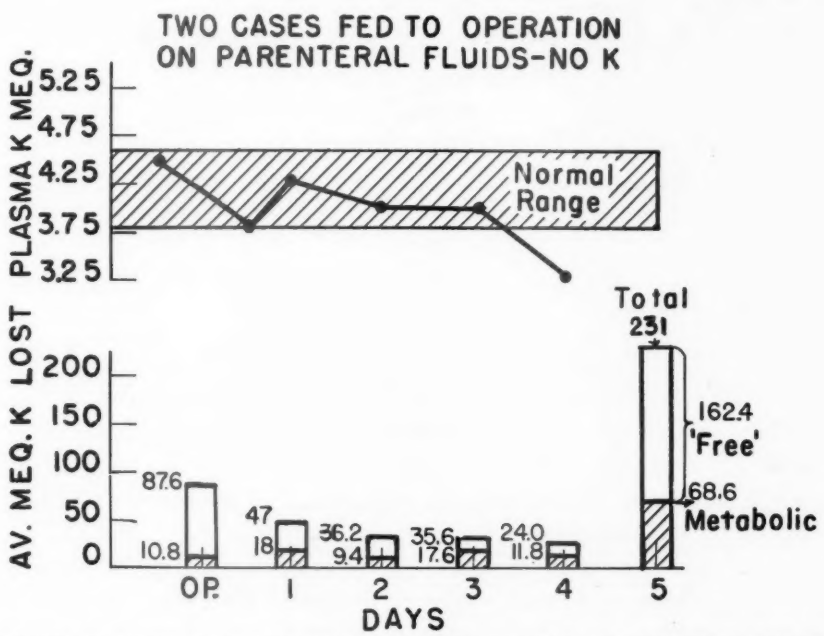


Fig. 2.—Patients in Group I on controlled diet until operation and potassium free parenteral fluids postoperatively, illustrating average plasma K level and daily and total K loss.

chloecystectomy. The average intake for these two patients was 162 meq. of sodium and 149 meq. of chloride ion per twenty-four hours, the slight discrepancy consisting of the small amount of sodium present in the amino acid preparations used. The details of the nitrogen balance studies in these metabolism unit cases will be presented in a forthcoming paper,[54] but in general the regimen was calculated to provide 85 Gm. of protein equivalent (13.5 Gm. nitrogen) and 18 calories per kilogram in the parenteral fluids used.

The total volume of fluid given averaged 50 c.c. per kilogram per day. Fig. 2 shows that these patients maintained plasma potassium levels within

the normal range until the final day when they fell slightly below normal. Also illustrated is the marked loss of potassium in the first twenty-four hours as reported by Iob, Berry, and Cooper[34, 35, 36] with total potassium far exceeding catabolic expectation (nitrogen in grams × 2.75). The potassium lost per day decreases in succeeding days but more potassium is lost throughout the period than is accounted for by catabolism, and the total shows that the loss of potassium averaged 231 meq. of which 162.4 meq. represented "free" potassium, a ratio of "free" to catabolic K of 2.3 to 1.

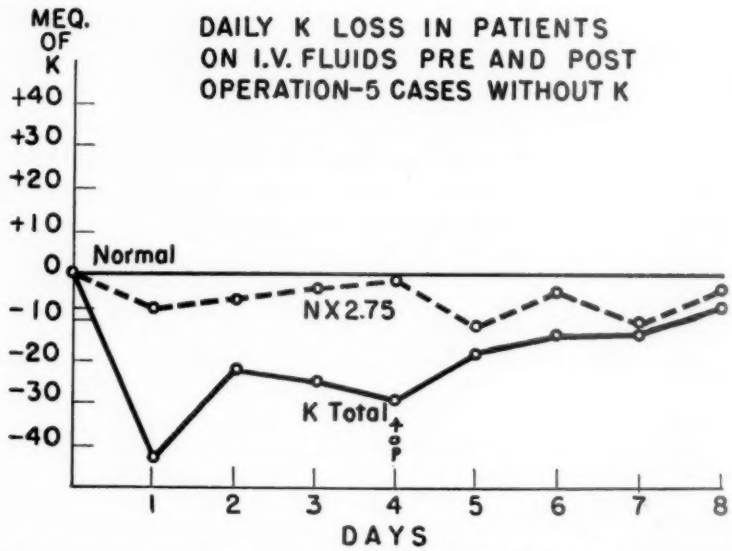


Fig. 3.—Patients in Group II on parenteral fluids for three days preoperatively, day of operation, and four days postoperatively. Average daily losses of potassium together with expected losses from nitrogen balance. No potassium given.

Figs. 3 and 4 illustrate the daily potassium balance in Groups II and III, patients who were placed on parenteral fluid regimes three days preoperatively after ten days of controlled oral intake on balance studies. Group II received no potassium parenterally while Group III received an average of 50.7 meq. of potassium chloride parenterally per day. There were three ventral herniorrhaphies, one umbilical herniorrhaphy, and one cholecystectomy in Group II (Patients M. M., C. C., A. C., M. B., and G. S.) while Group III consisted of four cholecystectomies, one with a common duct drainage with T tube (Patients S. A., A. R., J. B., and M. B.). All but one were women. Group II received an average of 145 meq. of Na and 132.6 meq. of Cl per day, while Group III received 151 meq. of Na, 160 of Cl and 50.7 of K. Both groups received 13.5 Gm. of nitrogen as 10 per cent amino acids. Group II (Fig. 3), given no potassium, shows a large loss of potassium on the first day of infusions, and a consistent loss diminishing with time, but always exceeding that expected from nitrogen deficit. Group III given potassium (Fig. 4) shows an average loss on the first day of infusions, and a loss on the day of operation and the first postoperative day, and thereafter shows a slightly positive potassium balance. The figures show the average for all the cases in each group. All patients in both groups were operated upon on the fourth day.

Figs. 5 and 6 show cumulative averages for the same groups and show the contrast between the debt of 170 meq. averaged by Group II and the slightly positive balance achieved by Group III. The amount of potassium excretion expected on the basis of nitrogen debt was almost the same in both groups averaging 46.8 meq. in the group without potassium and 49.2 meq. in the potassium infused group. The large excess of potassium loss over what is accountable from catabolism is again obvious in the group which did not receive potassium. It is interesting that in these patients with relatively atraumatic procedures, operation appeared to produce only a slight or transient increase in the rate of potassium excretion.

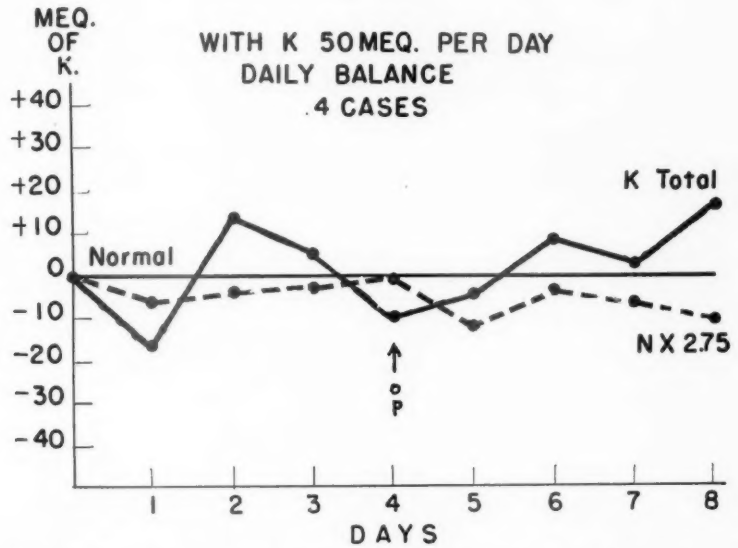


Fig. 4.—Patients in Group III with same program as Group II except for 50.7 meq. of potassium ion per day given parenterally. Average values of daily K losses together with expected loss from nitrogen balance.

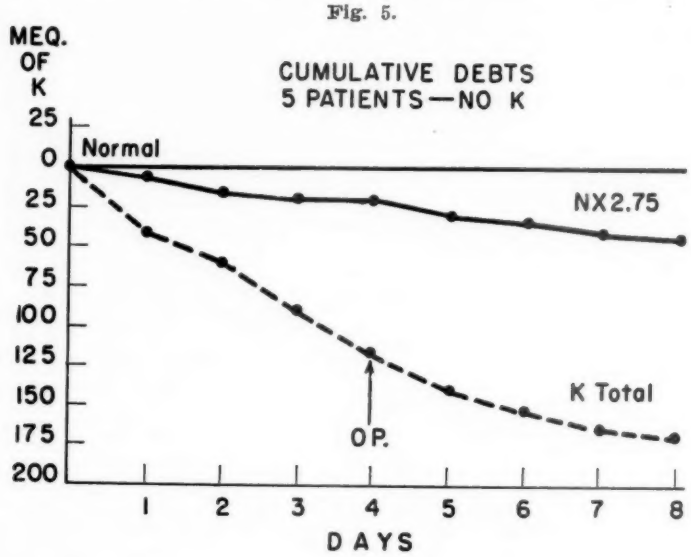
The plasma potassium averages are shown for Groups II and III in Fig. 7. The group which did not receive potassium displayed a steady fall in plasma concentration, while the group receiving potassium maintained normal levels with the exception of the operative day where both pre- and post-operative levels were below normal. The slope of the curve off all of plasma potassium roughly parallels the deficit in the untreated group.

Potassium Equilibrium in Miscellaneous Surgical Conditions.—A group of 54 patients (Group IV) were studied from the general surgical wards, most of whom were subjected to major surgical procedures. Potassium determinations were done either to assist in fluid and electrolyte balance, or to attempt to evaluate and correct developing imbalance. None of these patients had received any parenteral potassium or any potassium-containing food or fluids by mouth since operation. Fig. 8 indicates average plasma potassium levels (solid line), while the vertical bars represent highest and lowest values found. In general, although not invariably, acute symptoms suggestive of potassium deficiency appeared in cases with levels of 2.3 meq. per liter or lower. Of 8 patients who

maintained normal potassium levels at an average of 2.8 days, it is interesting to note that four had gastric resections, three appendical abscesses, and one multiple hepatic abscesses. Clinical dehydration of moderate degree was present in some of the remaining cases but did not appear to prevent a fall in the plasma potassium level.

In addition to the loss of potassium through renal excretion, some surgical patients have an additional drain through water and electrolytes lost from the gastrointestinal tract. Figs. 9 and 10 from a previous paper[55] show observations that have been made on gastrointestinal tract drainages in seriously ill and often depleted patients. These values show that concentrations of electro-

Fig. 5.



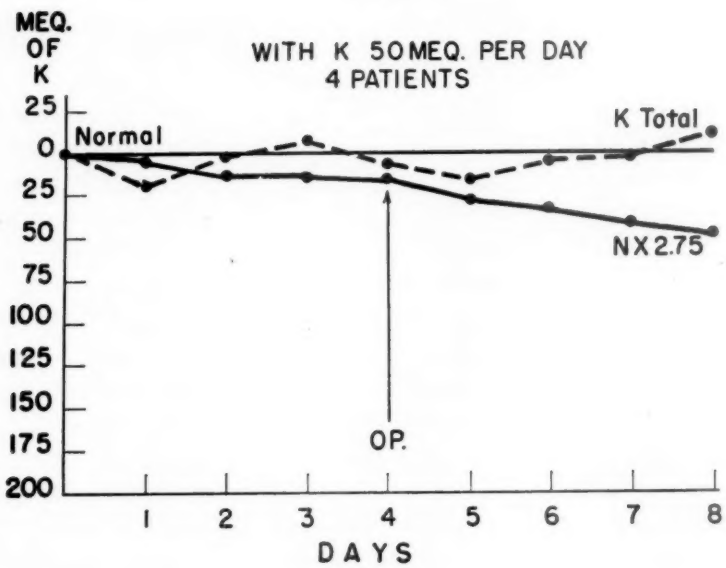


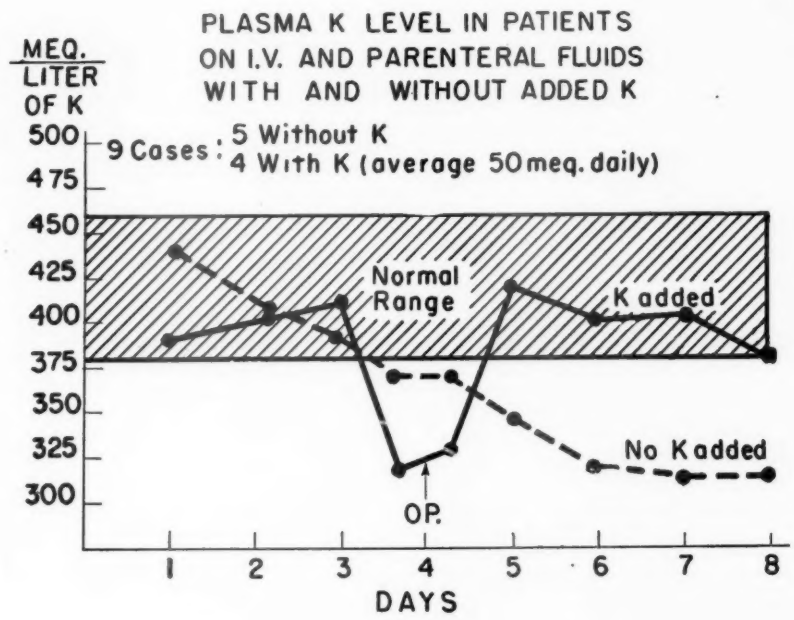
Fig. 6.

Fig. 5.—Cumulative average potassium balance and expected loss from nitrogen balance of Group II patients (Fig. 3).

Fig. 6.—Cumulative average potassium balance and expected loss from nitrogen balance of Group III patients given potassium (Fig. 4).

lytes in fluids lost are often surprisingly hypotonic and are subject to a very wide range of variation. In general the more depleted of electrolytes the patient is, the more hypotonic the secretions may be expected to be. Potassium losses from the stomach and the lower small bowel may be quite large, and doubt-

Fig. 7.



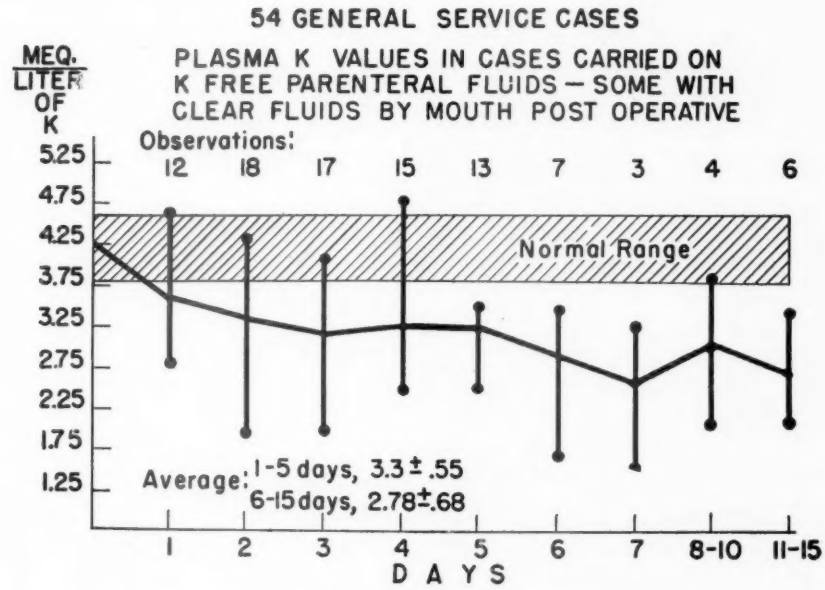


Fig. 8.

Fig. 7.—Average plasma potassium levels of patients in Group II (dotted line) and Group III (solid line) during treatment.

Fig. 8.—Patients in Group IV from General Surgical Service illustrating average plasma potassium levels and extremes observed in a group of fifty-four patients who had no potassium intake following major procedures.

less would be larger still if acute dehydration were present as well. It is easy to see how 100 meq. of potassium per day might be lost from an ileostomy or Miller-Abbott tube withdrawing 3,000 to 4,000 c.c. per day from the ileum. Values for normal urine are from patients in the preoperative control period on the metabolism service. The extremely low values of urinary sodium possible

Fig. 9.

G.I. TRACT LOSSES M.E.Q. PER LITER

	Na	K	Cl
GASTRIC (Fasting)	60.4 9-116	9.2 0.5-32.5	84.0 7.8-154.5
SMALL BOWEL (MA Suction)	111.3 82.-147.9	4.6 2.3-8.0	104.2 43-137
ILEOSTOMY (Recent)	129.4 105.4-143.7	11.2 5.9-29.3	116.2 90-136.4
ILEOSTOMY (Adapted)	46	3.0	21.4
CAECOSTOMY	52.5	7.9	42.5

Fig. 10.

BILE AND PANCREATIC FISTULAE

		Na	K	Cl
BILE		148.9 131-164	4.98 2.6-12	100.6 89-117.6
PANCREAS		141.1 113-153	4.6 2.6-7.4	76.6 54.1-95.2
URINE	Normal	40-90	20-60	40-120
	Path.	0.5-312	5-166	5-210
TRANSUDATES		130-145	2.5-5.0	90-110

Fig. 9.—Average figures and ranges observed for sodium, potassium, and chloride ions per liter in gastrointestinal tract fluids from ill patients on the General Surgical Service.

Fig. 10.—Average figures and ranges observed for sodium, potassium, and chloride ions from biliary and pancreatic fistulas together with ranges observed in urine and transudates. (Figs. 9 and 10 from Lockwood and Randall, Bull. New York Acad. Med., p. 234, April, 1949.)

postoperatively, as well as the high potassium, are of interest. Fig. 11 illustrates some observations made on patients with Miller-Abbott tubes given parenteral fluids but not operated upon. These patients had intestinal obstruction and various degrees of dehydration on admission. The rapid fall in plasma potassium levels we believe reflects potassium deficiency which rapidly becomes manifest in most cases on rehydration without potassium.

Hypochloremic Alkalosis.—A number of the general surgical service patients were studied who developed the chemical picture of hypochloremia with alkalosis.

The symptoms that attended were very variable, but in general tended to correspond to those reported by Ireneus[38] and by Ariel, Abels, Pack, and Rhoads.[37] Fig. 12 shows the chemical findings in fourteen such patients (Group V), ten of whom recovered after an oral diet, sometimes supplemented with potassium salts, was commenced, and four of whom had to be

Fig. 11.

BEHAVIOR OF PLASMA K IN PATIENTS WITH MILLER-ABBOTT TUBES, NO OPERATION, NO K

Case	DAYS 0	1	2	3	4	5	6	7
1	4.2	-	2.5	-				
2	4.1	-	-	-	-	3.0	-	2.8
3	-			3.1				
4	4.9	3.6	-	3.7	3.5	-	-	-
5	-	2.9	-					
6	-	3.6						
7	-	3.3	2.8	-				

A Comparison of 10 Patients Recovering on Diet, Some with Oral K and 4 Patients with Parenteral K Correction of Alkalosis

	DIET	I. V.
Days on K Free Parenteral Fluids	6.0	5.0
High $(HCO3)^+$ Average	36.5	37.3
Low Cl^- Average	89.6	89.5
Average PLASMA Na^+	138.5	141
Average PLASMA K^+	2.6	2.6
Days to Normal Values	6.4	3.5

None of these patients had plasma proteins below 5.9

Fig. 12.

Fig. 11.—Some observations of plasma potassium levels in patients with Miller-Abbott tubes showing effect of parenteral fluid administration following dehydration, together with large losses of fluid from the gastrointestinal tract.

Fig. 12.—Patients with hypochloremia and alkalosis, illustrating days postoperatively to onset, average plasma values, and days to recovery of normal chemical values in patients who recovered on diet, and those treated with parenteral potassium chloride.

maintained on parenteral fluids and who responded to the intravenous administration of potassium chloride. The number of days between operation and the establishment of the chemical diagnosis was very similar in the two groups, as were the low chloride and high bicarbonate findings. All of these patients had been generously infused with sodium chloride, some with excessive amounts, and all had developed hypochloremia and alkalosis in spite of, or in part because of, such therapy. It should be noted that the average plasma sodium levels were within normal range, and that the plasma potassium levels were low. None of these patients presented a marked hypoproteinemia. Three cases presented briefly will illustrate certain of these points.

CASE REPORTS

W. A. (920899) was a 58-year-old man who was admitted to the Presbyterian Hospital Aug. 26, 1948, with a chief complaint of 2½ months of increasing jaundice and pruritis, anorexia, and a weight loss of fifteen pounds. Past history was noncontributory; there was no history of fatty food intolerance or previous jaundice. Laboratory work-up revealed no anemia, a serum bilirubin of 9.6 mg. per cent, and alkaline phosphatase of 10.7 Bodansky units. Hematocrit was 43.5 and serum proteins 7.13 Gm. per cent. Cephalin flocculation was negative. Duodenal drainage revealed no bile and no blood cells. X-ray examination showed a postbulbar constriction of the duodenum. The patient had consistently clay-colored stools and dark urine and was clinically jaundiced. Exploration was carried out on Sept. 3, 1948, and a carcinoma of the ampulla of Vater involving the common duct and part of the head of the pancreas was found. A pancreatoduodenectomy with choledochojejunostomy and gastrojejunostomy was performed. A sump drain was placed to the cut end of the pancreas in view of the fact that no ducts could be found and the marked edema of the pancreas prevented anastomosis to the jejunal loop. The procedure was well tolerated, and on the operative day the patient was given a total of 2,300 c.c. of blood and 1,500 c.c. of saline solution. A nasogastric tube was placed and postoperatively drained 2,800, 2,100, 5,200, and 3,600 c.c. in the first four postoperative days. Of this about one-half was water taken by mouth. The patient was maintained on a parenteral infusion intake averaging 3,200 c.c. per day, of which in the first three days 1,500 c.c. per day were saline solution and on one occasion 500 c.c. of M/6 sodium lactate were given. Urine output was satisfactory, averaging 1,300 c.c. per day. By the fourth postoperative day the patient complained of marked thirst, yet vomited around the tube when he took water by mouth. He was drowsy, mildly distended, uncomfortable, and showed a moderate amount of serosanguineous drainage from the wound. Laboratory data on this day showed: hematocrit 45.0 with plasma proteins of 6.93, serum sodium 142 meq. per liter, potassium 2.5 meq. per liter, HCO_3 38.3 meq. per liter, and chloride 82.6 meq. per liter. The urine contained 57.5 meq. per liter of sodium and 14.8 meq. per liter of potassium, and the drainage from the wound 152.5 meq. per liter of Na and 1.9 meq. of K per liter. It was decided that he had a potassium deficiency, probably with an associated chloride deficiency as the result of the gastric and upper small bowel suction. Accordingly, he was started on a regime which gave him 30 meq. of KCl that day and 60 meq. per day for the two succeeding days, together with an average of 250 meq. of sodium chloride in a total volume of 3,500 c.c. since the fistula had begun to drain large volumes of pancreatic juice. The following day he considerably improved, nasogastric drainage had dropped to 2,100 c.c. with an oral intake of 1,600 c.c. of water, and plasma sodium had fallen to 131 meq. per liter with plasma potassium remaining at 2.5 meq. per liter. Chloride had risen to 90 meq. per liter and bicarbonate had fallen to 29.8 meq. per liter. The following day (sixth postoperative) the serum sodium was 130 meq. per liter, potassium 2.9 meq. per liter, HCO_3 27.2 meq. per liter, and chloride 93 meq. per liter. There was drainage of 1,200 c.c. of pancreatic juice and the urinary output was 1,000 c.c., which contained but 9.3 meq. of the 60 meq. of potassium administered. He retained most of an oral intake of full fluids with nasogastric tube clamped, and the following day the tube was removed. By the seventh day the serum sodium was 137 meq. per liter, potassium 4.1 meq. per

liter (with larger amounts in the urine), HCO_3 27.2 meq. per liter, and chloride 96.6 meq. per liter in plasma. He was placed on a soft diet on the eighth day and on a regular diet on the eleventh, and was able to keep up with the loss of pancreatic juice electrolytes with the aid of 6 Gm. per day of enteric coated sodium chloride by mouth until the forty-sixth postoperative day, at which time the fistula was anastomosed to jejunum. He made an uneventful recovery from this second procedure and was last seen March 16, 1949, having gained ten pounds in weight and feeling very well.

M. C. (794354) was a 48-year-old woman, a known diabetic, who was admitted to Presbyterian Hospital Aug. 11, 1948, in mild acidosis, and while in the hospital developed signs of obstructive jaundice. The common duct was explored and T-tube drainage instituted. However, postoperatively she developed an ileus requiring Miller-Abbott tube intubation, and by the fifth postoperative day had definite signs of intraperitoneal infection localized to the right upper quadrant. The common duct was re-explored and a bile peritonitis secondary to leakage around the T tube was found. By the fourth day after the second procedure, having been given only dextrose in saline solution, dextrose in water, and some amino acids parenterally, there was moderate distention and a hematocrit of 44.5 with plasma proteins of 6.75 with a plasma HCO_3 of 36.6 and chlorides of 95.3. The following day she was started on feedings by mouth, but suddenly that evening became extremely weak, listless, and apathetic, and was hardly able to move or speak. Blood pressure did not fall, and the skin was warm and dry. Emergency electrolyte determinations at this time showed HCO_3 of 38.6, chlorides of 94.5, sodium of 138.5, and potassium of *1.6 meq. per liter* in plasma. She was given 60 meq. of potassium chloride parenterally within the next twenty-four hours, and responded quickly with marked increase in muscular strength and vigorous objections to further parenteral fluid administration. She was able to tolerate food by mouth, and so was given supplemental potassium by mouth and made a slow but uneventful recovery, HCO_3 and chloride values reaching 30.6 and 97.5 meq. with sodium of 138.5 and potassium of 3.6 meq. per liter in the plasma by the ninth day after the acute episode.

P. J. (726666) was admitted to Presbyterian Hospital June 2, 1948, with symptoms and x-ray evidence of acute intestinal obstruction which subsided promptly with Miller-Abbott intubation, and she was discharged on the seventh day to continue a diagnostic work-up in the outpatient department; however, she returned ten days later, again with obstruction, was again decompressed with a Miller-Abbott tube, and a barium enema revealed a constricting lesion in the ascending colon which at operation proved to be a carcinoma. Accordingly, an ileocolectomy and ileotransverse colostomy was done. Postoperatively she began to vomit, in spite of the tube, on the third postoperative day. The tube was then withdrawn to the stomach, and would not go into the duodenum again. She continued to vomit an average of 1,500 to 2,000 c.c. of gastric and upper small bowel contents a day for the next eight days, and x-ray examination suggested a high jejunal obstruction. By the fourteenth postoperative day, despite large volumes of parenteral fluids, the urine output had fallen to 355 c.c. and the following day was 250 c.c. with a beginning rise in serum urea nitrogen. She was mildly edematous, extremely uncomfortable, and vomited and had lost through the Miller-Abbott tube a total of 3,650 c.c. without oral intake. Plasma sodium was 141.5 meq. per liter and potassium 2.4 meq. per liter with HCO_3 34 meq. per liter and chlorides 94.7 meq. per liter. Hematocrit was 42.4 and plasma proteins 8.38 Gm. per cent. She therefore represented a picture of dehydration, oliguria, and peripheral edema, with low plasma potassium, alkalosis, and mild hypochloremia. A blood volume done this day showed a total volume of 70 c.c. per kilogram body weight with 29 c.c. red cells and 41 c.c. plasma. A plan was therefore made to rehydrate her, replace as much of the potassium deficit as possible, and then restore the blood volume by transfusion before re-operating to discover the cause of the upper small bowel obstruction. Through a misunderstanding only 4,350 c.c. of parenteral fluids were given the following (fifteenth postoperative) day and as a result she excreted only 140 c.c. of urine in the following twenty-four hour period. She was given 2,000 c.c. of a mixture of potassium and sodium chloride containing a total of 60 meq. of K, 1,350 c.c. of

saline solution, and 1,000 c.c. of an amino acid mixture containing 34 meq. of sodium chloride per liter.

The sixteenth day she was given 6,500 c.c. parenterally including 3 liters of sodium-potassium chloride mixture, 1,000 c.c. of dextrose in saline solution, 1,000 c.c. of amino acids, and 1,500 c.c. of 5 per cent dextrose in water. She received 90 meq. of K. In the next twenty-four hour period she voided 1,360 c.c. of urine, and serum sodium was 136.5 meq., potassium 2.9 meq., chlorides 104.2 and HCO_3 27.2 meq. in plasma. She was then carried on maintenance fluids of from 3,500 to 4,000 c.c. of parenteral fluids a day for the next three days, and was given three blood transfusions to restore the blood volume. She voided 2,800 c.c., 1,775 c.c., and 1,950 c.c. in these three days and the edema disappeared. This was accompanied by a fall in hematocrit and plasma protein to 40 and 6.97, respectively, on the eighteenth day. She was given an average of 20 meq. of K per day during this period, which was not enough, for her plasma K which was 3.9 meq. per liter on the eighteenth day fell to 2.4 on the twentieth day, together with drop in urine output to 625 c.c. and a rise in hematocrit to 46.4, with proteins of 7.8 Gm. per cent. This was treated with an additional amount of parenteral fluids and 90 meq. of K, and on the twenty-first postoperative day exploration was carried out again and an intussusception of the proximal jejunum found and resected. An end-to-end anastomosis and gastrojejunostomy were performed. It was noted that the bowel, which had been generally edematous at the first operation, was much less so at the second. One liter of blood but no potassium was given the operative day, and the following morning plasma sodium was 128 meq., potassium 3.0, and chloride 91.8 meq. The Miller-Abbott tube, which had been placed past the jejunal anastomosis, drained 2,000 c.c. and, in addition, she vomited 500 c.c. the first postoperative day. The hematocrit was 51.5 and plasma proteins 6.55, serum sodium 132, and potassium 4.05 meq. per liter. She was given 30 meq. of K this day with 5,000 c.c. of water, 2,000 of it saline solution, and the following two days was given 90 meq. of potassium in 3 liters of potassium and sodium chloride mixture together with 1,000 c.c. saline and glucose and 1,000 c.c. glucose in water. The urinary output remained about 400 c.c. a day for four days while tube drainage averaged 3,000 c.c. net. The serum analyses on the third postoperative day showed sodium 135 meq., potassium 2.6 meq., chloride 93.8, and HCO_3 28.7 meq. per liter. She put out 2,300 c.c. and 2,775 c.c. of urine on the fifth and sixth postoperative days, and on the sixth day, having received 27,500 c.c. of parenteral fluid and 270 meq. of potassium since operation, the plasma sodium was 140 meq., potassium 3.5 meq., chloride 98.4 meq., and HCO_3 24.2 meq. per liter. Hematocrit was 42 and plasma proteins 5.77. She was started on fluids by mouth on the seventh postoperative day, the tube was taken out the ninth day, and she went home on the twentieth day. She has remained well since that time.

DISCUSSION

It is obvious from a review of the literature that many of the conditions which have been reported as leading to potassium deficiency states can, and often do, exist in surgical patients. Losses as the result of reduction or elimination of potassium intake through the gastrointestinal tract are almost the rule, and if one adds the effects of infusions[31-36] with increased excretion of potassium, and its possible withdrawal in glycogenesis, as well as the effects of saline solution in increasing potassium losses, as observed by Stewart and Rourke,[33] and Iob,[34] almost every postoperative surgical case becomes a candidate for potassium deficiency. Dehydration is certainly present at some time in many surgical conditions, and as Elkinton and Winkler and their associates have shown,[14, 15, 16, 18] potassium losses are very large in dehydration, and in the presence of excess sodium,[19] the potassium being excreted by the kidney as it is moved out with intracellular water, and often displaced by sodium within the cell. Subsequent rehydration with saline solution results in

the appearance of a marked potassium deficit as has been demonstrated so well by Darrow[6] in the rehydration of infants dehydrated by diarrhea, as well as by Butler[10] and others[11, 12, 13] in rehydration in diabetic acidosis.

Darrow[45] has suggested that changes in equilibrium result in potassium deficiency, and has demonstrated in experimental animals that induced alkalosis[27] results in lowered cell potassium with a direct relationship existing between the amount of sodium in the cell and the plasma bicarbonate. Changes in equilibrium certainly occur in pyloric obstruction, where chloride ion loss predominates, in biliary or pancreatic fistulas where sodium loss is dominant, in large volume losses from the small bowel, or as diarrhea. Disturbances may also occur in the postoperative period through depression of renal function, with sodium retention as described by Coller,[40] in which connection we have noted postoperative sodium excretion levels as low as 0.5 meq. per liter of urine in spite of normal plasma sodium levels and with simultaneous high levels of K excretion.

Gastrointestinal tract losses may be a primary route of a considerable loss of potassium as we have previously reported[55] and are illustrated in Figs. 9 and 10, and surgical patients often have large volumes of gastrointestinal tract losses with dehydration. The extent of these losses is well illustrated by Abbott, Mellors, and Muntwyler in experimental work with dogs,[56] and in diarrhea studies by Butler[3] and Darrow.[4, 6, 7]

Long and traumatic surgical procedures appear to be followed by an increase in potassium losses as compared to those occurring in herniorrhaphies or in normal subjects on infusions as studied by Berry[35] and Cooper.[36] Thus, the surgical patient may have many simultaneous factors operating to produce losses in potassium which may reach considerable magnitude.

In the studies on patients from our metabolic unit, it will be noted that we have confirmed the reports of Iob and her associates[34] that in minor surgical procedures, at least, placing a patient on parenteral fluids has more of an effect on potassium loss than does the operation itself. Fig. 3 (Group II) shows the large loss in the first twenty-four hours, with smaller but definite losses throughout the period. Operation on the fourth day produced a slight increase in the loss, but it did not reach the magnitude of that of the first day on infusions. As reported by Berry[35] and others, the amount of potassium lost far exceeds that expected from the ratio of nitrogen to potassium in cells. We have used a figure of 2.75 meq. of potassium per gram of nitrogen as a compromise between 2.87 calculated from days 2 to 11 in Benedict's data[1] and the lower figures discussed by Berry.[35] In Group II, patients who did not receive potassium, the ratio of unassociated potassium is 2.6 to 1 of potassium associated with nitrogen loss. This checks well with 2.3 to 1 noted in the Group I patients who were carried on parenteral fluids only, from operation on, as described in Fig. 2.

The administration in infusions of 50 meq. of K a day as potassium chloride made a striking difference in the potassium balance of similar groups of patients, as can be seen by comparing metabolic Groups II and III (Figs.

3, 4, 5, and 6). Potassium losses occurred only during the first twenty-four hours, the day of operation, and the first postoperative day in Group III as shown in Fig. 4, and the cumulative balance was actually positive for potassium during the eight days. The nitrogen losses, however, were unaffected and are very similar for the two groups. This dissociation of nitrogen loss and potassium balance suggests that potassium-sodium relationships are more significant under these circumstances. Unfortunately, muscle biopsies have not been done with initial controls to confirm that intracellular sodium actually decreased in the potassium-treated patients as seems probable.

We have been particularly interested to see whether plasma potassium values, which are easily obtained, would be of value in estimating potassium deficit. It seems definite that there is a drop in the plasma potassium levels in the patients receiving no potassium that did not occur in patients who received parenteral potassium in prophylactic amounts. Fig. 7 shows the comparative figures for Groups II and III. In Group II patients the amount of potassium excreted unassociated with N losses decreases with time, and it appears that they tend to level off at a lower plasma level and may not develop signs of acute potassium deficiency even during an extended period on parenteral fluids. However, when more major procedures are involved, and dehydration, gastrointestinal tract losses, or perhaps the injudicious use of saline solution enters the picture, together with a reduction in the capacity of the kidney to maintain balance, some patients have potassium losses which are very large and develop signs of acute deficiency. Fig. 8 shows the trend and extremes of plasma potassium levels in a series of patients from the general ward service; it will be noted that plasma potassium concentrations sometimes reached levels representing a reduction of 60 to 70 per cent of normal values. In general it may be stated that symptoms and chemical findings of imbalance seem to appear at levels of 3.0 meq. and that the more severe expressions of deficiency appeared with levels of 2.6 meq. per liter or less. The two cases of extreme muscular weakness that we have observed (one of whom, M. C., is briefly reported upon) had levels at the time of the weakness of 2.0 or below. However, there seems to be considerable variation in the level at which any particular patient will manifest symptoms so the plasma potassium level becomes a definitive index of significant deficiency only when below 2.6 meq. per liter, even though levels below 3.5 meq. per liter may be suggestive. Fig. 11 shows that efforts to rehydrate a patient with dehydration associated with continuing gastrointestinal losses may result in low plasma potassium levels in the absence of potassium replacement.

The symptoms of potassium deficiency are divisible into two groups. The first of these is the acute syndrome of skeletal muscle weakness, sometimes with paralysis of the intercostals, and diaphragm as described by Holler,[11] Martin and Wertman,[12] and Nicholson and Branning[13] in diabetic acidosis with rehydration, and by Brown, Currens, and Marchand[20] in chronic nephritis. This syndrome has been observed by us in two patients and perhaps in early stages in two more. The patient M.C. illustrates this manifestation.

More commonly, however, we have seen a rather diffuse symptom complex resembling that described by Ariel, Abels, Pack, and Rhoads[37] and Ireneus,[38] consisting of the onset from the fourth to the ninth postoperative day of drowsiness, languor, chronic ileus with moderate distention, anorexia, and weakness, frequently accompanied by some peripheral edema, oliguria, and hemoconcentration. Not all symptoms are present in any one case, and it is evident that the pattern is not altogether specific. Usually accompanying this syndrome are a low plasma chloride, high plasma bicarbonate, and a low plasma potassium. It has been noted by Ariel that these patients improve rapidly when they begin to eat, and Fig. 12 documents fourteen such patients (Group V), ten of whom (including M. C.) recovered on diet, some with supplemental potassium. The increase in dietary intake in these patients is usually slow, and it was observed that the time required for chemical restoration of normal bicarbonate and chloride levels averaged 6.4 days after food was started. Four patients, including P. J., had to be carried on parenteral fluids and responded symptomatically and chemically to the parenteral administration of from 60 to 90 meq. of potassium per day, thus leading to the conclusion that hypochloremic alkalosis is in some way associated with potassium deficiency and is in large part a primary potassium deficiency state. We have been using potassium-containing solutions on the surgical service at Presbyterian Hospital for a little more than one and one-half years, and employ two solutions. The first of these consists of 110 meq. of sodium, 30 meq. of potassium, and 140 meq. per liter of chloride ion in distilled water.* The second consists of 30 meq. of potassium and 30 meq. of chloride ion per liter in 5 per cent dextrose and water (2.23 Gm. KCl per liter) and was developed on the surgical service to fulfill the need for a solution containing potassium but not sodium. Both are administered by standard infusion equipment at a rate not exceeding 1 liter per hour, with care being exercised to see that the infusion does not run in a steady stream when first started. We have not exceeded this concentration of potassium, although Darrow[6] has used 40 meq. per liter and routinely uses 35 meq. per liter.

Certain specific contraindications to the use of these solutions are observed. The solutions are not used in acutely dehydrated patients until rehydration is well under way, the hematocrit is falling, and urinary output is definitely rising unless (as was the case with patient P. J.) we have laboratory evidence to show that the patient has a low plasma potassium level. We do not use the solutions in patients with acute or chronic renal disease unless the serum potassium is low and the indications are definite, and then only with great caution; furthermore, solutions of potassium are not used during, or for twenty-four hours after, major operative procedures. Following these precautions, we have not observed any evidence of potassium intoxication, and the solutions are now in general use on the surgical service.

Therapeutic administration consists of the use of from 60 to 120 meq. of potassium a day with due regard to the total fluid volume permissible in

*(2.23 Gm. KCl, 6.44 Gm. NaCl per liter) This solution was first introduced to the hospital by Dr. G. H. Mudge of the Medical Service.

the patient being treated. Such amounts are given to patients with documented electrolyte imbalance and low serum or plasma potassium levels, particularly those that demonstrate hypochloremia and a high serum bicarbonate. Similar levels of administration are sometimes necessary to replace potassium lost in extensive drainage from the gastrointestinal tract through Miller-Abbott tube or fistula, and an effort is made in these cases to determine the twelve or twenty-four hour losses from all sources and quantitatively to replace sodium, potassium, chloride, and bicarbonate ions. In these cases the flame photometer is essential for rapid and accurate determinations of concentrations. Plasma and urine potassium levels are recorded daily, and as these rise, the amount of potassium administered is accordingly reduced.

In the past year we have been using potassium solutions prophylactically, starting the second postoperative day in patients that we expect to carry on parenteral fluids for four or more days with not more than clear fluids by mouth, and by this means we appear to have reduced the number of patients who have developed edema and alkalosis, and we have certainly improved potassium equilibrium in these patients. On these grounds we feel that such a program has a rational basis and will be increasingly useful. However, it is agreed that further work is needed before routine prophylactic use of potassium can be advised. The amount administered prophylactically is usually 30 meq. of potassium per day. Rigid limitation of sodium infusions is an important part of preventing potassium depletion and edema, since excessive sodium displaces intracellular potassium, and saline solution is restricted to a maximum of 500 c.c. per day unless there are definite indications for the use of more than this amount. In this connection, the recommendations of Coller and his associates[40] are generally observed.

We have found very useful for oral therapy a mixture of potassium acetate, bicarbonate, and citrate, 1 Gm. of each made up to a volume of 8 c.c. with water. Such a mixture contains 27 meq. of potassium in 8 c.c. and can be given in doses of 4 c.c. three times a day well diluted in fruit juice to supplement the potassium intake of patients who are tolerating fluid feedings. This sometimes eliminates the necessity for infusions.

Low plasma potassium levels are accompanied by definite electrocardiographic changes in man, as reported by Holler[11] and Brown, Currens, and Marchand.[20] Darrow and Miller[57] have shown definite pathologic changes in the heart muscle of rats with low serum potassium and alkalosis as the result of desoxycorticosterone administration. No definite pathologic changes attributable to potassium deficiency are known to occur in patients other than edema of cells in which sodium has replaced potassium, but it is reasonable to assume that changes take place in cells as the result of the marked water and electrolyte imbalances that have been observed, of which potassium deficiency constitutes an important part. We feel that the therapeutic and prophylactic use of potassium salts in certain surgical conditions will probably be increasingly indicated to replace or anticipate deficits which have

been demonstrated to occur. However, the management of potassium requirements must always be integrated with an over-all program of physiologic water and electrolyte replacement.

SUMMARY

The potassium balance and serum potassium levels were studied in three groups of patients observed in a surgical metabolism unit. One group was maintained on food by mouth until operation and then carried on parenteral fluids including amino acids but without added potassium for the operative day and four days thereafter. The second group was placed on the same parenteral fluids including amino acids but these were given for three days preoperatively as well as postoperatively. The third group was similar to the second except for the addition of 50 meq. of potassium per day parenterally. The first two groups demonstrated a consistent loss of potassium in excess of that associated with nitrogen. The largest losses occurred on the first day on parenteral fluids. Operation increased the potassium loss in the second group on the operative and first postoperative days, but the magnitude of the losses was below that occurring on the first day of parenteral fluid therapy. The third group given potassium showed losses on the first day of parenteral fiuids and on the operative and first postoperative days, but maintained a positive potassium balance for the period. Plasma potassium levels fell below normal in the second group but not in the third, except for the operative day.

Data are presented for a miscellaneous group of surgical cases in which postoperative plasma potassium levels were observed. There was wide variability, but a marked fall below normal in most cases. It is suggested that marked deviations in the plasma potassium level may serve as an approximation of the degree of potassium deficit.

Data are presented from fourteen cases of hypochloremic alkalosis together with brief reports of three cases. It is shown that this condition responds both to oral intake of food and to the parenteral administration of potassium chloride, although it is refractory to, and made worse by, sodium chloride. The features of this syndrome are discussed, and it is concluded that hypochloremic alkalosis is probably a potassium deficiency state.

The therapeutic and prophylactic uses of potassium salts in certain surgical conditions are discussed, and methods and precautions in their administration are outlined.

This work would not have been possible without the valuable assistance of the nursing and technical staff of the Surgical Metabolism Unit, including Miss Florence Schorske, Miss Rita Lipton, Miss Emily Cragin, Mrs. Hilda Carter, Miss Helen Pandelakis, Miss Charlotte Richardson, and Miss Edith Rosenblad.

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OBSERVATIONS IN JEJUNAL ALIMENTATION

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A CRITICAL feature of the management of patients facing radical surgery is the correction of malnutrition, if it exists, and the active maintenance of adequate feeding.[1] There are four possible ways of accomplishing these aims: (1) Oral ingestion of a suitable diet; (2) gavage feeding through an orally introduced rubber tube whose tip lies either in the stomach or in the upper jejunum; (3) parenteral feedings through a vein or the subcutaneous tissues; (4) feeding into a surgically constructed jejunostomy. With our present-day facilities it is next to impossible to satisfy basic nutritional requirements by parenteral means alone. It is generally agreed that food taken directly into the upper gastrointestinal tract will be utilized with maximum efficiency. If the patient can be induced to eat enough of the right type of food, it is the best means of satisfying his nutritional needs. Unfortunately, the very patients with the most severe nutritional disturbances are those usually incapable of tolerating a sufficient oral intake because of severe anorexia, vomiting, or organic obstruction.

The construction of a jejunostomy is a simple surgical procedure.[2] Jejunostomy feedings have the advantage of direct absorption from the intestinal tract, and are less annoying to the patient than gavage feedings through a tube maintained in the nasopharynx for a number of days. Although the advantages of jejunostomies for feeding have been strongly supported by some surgeons,[3-7] why have most surgeons so generally avoided them? This hesitancy to use jejunostomies has been due to two principal difficulties encountered in their actual use: first, the formulas usually recommended, although nutritionally excellent, tend to produce abdominal cramps and diarrhea, particularly in the first few days; second, the formulas themselves contain many complex constituents and are difficult to prepare in the average hospital diet kitchen. Therefore, in an effort to create a feeding which did not irritate the bowel and which would be simple to prepare, a series of experiments have been conducted in the laboratory and on the hospital wards. After the clinical trial of many different mixtures, the conclusion has been reached that commercial homogenized milk is the best basic constituent of a jejunostomy feeding.

The requirements for an ideal jejunostomy feeding mixture, as set forth by Stewart,[8] were regarded as the goal to be attained. These requirements may be summarized as follows:

Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 24-26, 1949.

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†Aid by grant from Comly Fund, Ohio State University.

1. Adequate amounts of all nutritional elements
2. Inexpensive and easy to prepare
3. Easily digested and absorbed with low residue
4. Drips easily by gravity
5. Not too high salt or osmotic concentration
6. Relatively stable in refrigerator for 48 hours

The Scott-Ivy pabulum[9] has been widely advocated[2, 4] because of its comprehensive nutritional composition. Nevertheless, even in the experience of its advocates[2, 4] it tends to cause diarrhea and cramps requiring paregoric or its equivalent. The Hollander formula,[10] one of the best devised, may produce diarrhea when first used, if the quantity is sufficient to maintain nutrition, even though jejunal tolerance may eventually develop. Although they are nutritionally complete, the fact that there are thirteen constituents in the Scott-Ivy pabulum[9] and twelve in the Hollander formula[10] renders it unlikely that they will be easily prepared by the average hospital kitchen staff. By way of contrast, Allen[11] has found a simple mixture of equal parts of milk and limewater given in small quantities to be well tolerated by the jejunum even in the first few days, but it is difficult to administer an adequate caloric content to maintain nutrition using this mixture alone.

The single food which most nearly seemed to meet Stewart's requirements[8] for an ideal feeding mixture was whole milk. Milk is universally available, of moderately high caloric value, almost complete nutritionally, and inexpensive. Recent investigators[8, 10] have avoided the use of milk as a base for jejunostomy feedings because of the apparent intolerance of the jejunum to the fat in whole milk. In preliminary investigations an attempt was made gradually to increase jejunal tolerance to the fat in whole milk by starting the feeding with skim milk and adding increasing proportions of whole milk. The milk was peptonized to increase its digestibility.[7] Three out of the five patients on whom this system was used developed severe diarrhea and abdominal cramps by the time they were receiving whole milk. This seemed to be an adequate demonstration that it was impractical to introduce undiluted whole milk directly into the jejunum in sufficient amounts to maintain nutrition in the average patient.

Since it was assumed that the fat in the milk was producing the diarrhea, attention was next turned to this aspect of the problem, and to the theories of fat absorption mechanisms. The generally acceped lipolytic theory of fat absorption (Fig. 1) assumes that all fat ingested in the diet is completely hydrolyzed by pancreatic lipase to glycerol and fatty acids. The fatty acids are then supposed to conjugate with bile salts to form a water-soluble fatty acid-bile salt complex which is absorbed through the membrane of the cells of the intestinal mucosa. In these cells resynthesis is thought to occur to form phospholipids and triglycerides, which pass both through the lymphatics and via the thoracic duct to the blood stream, and through the portal vein to the liver. Collaborators from the Department of Physiological Chemistry assisted in determining whether the work of Frazer[12-15] dealing with fat absorption as related to particle size might be applicable to this problem.

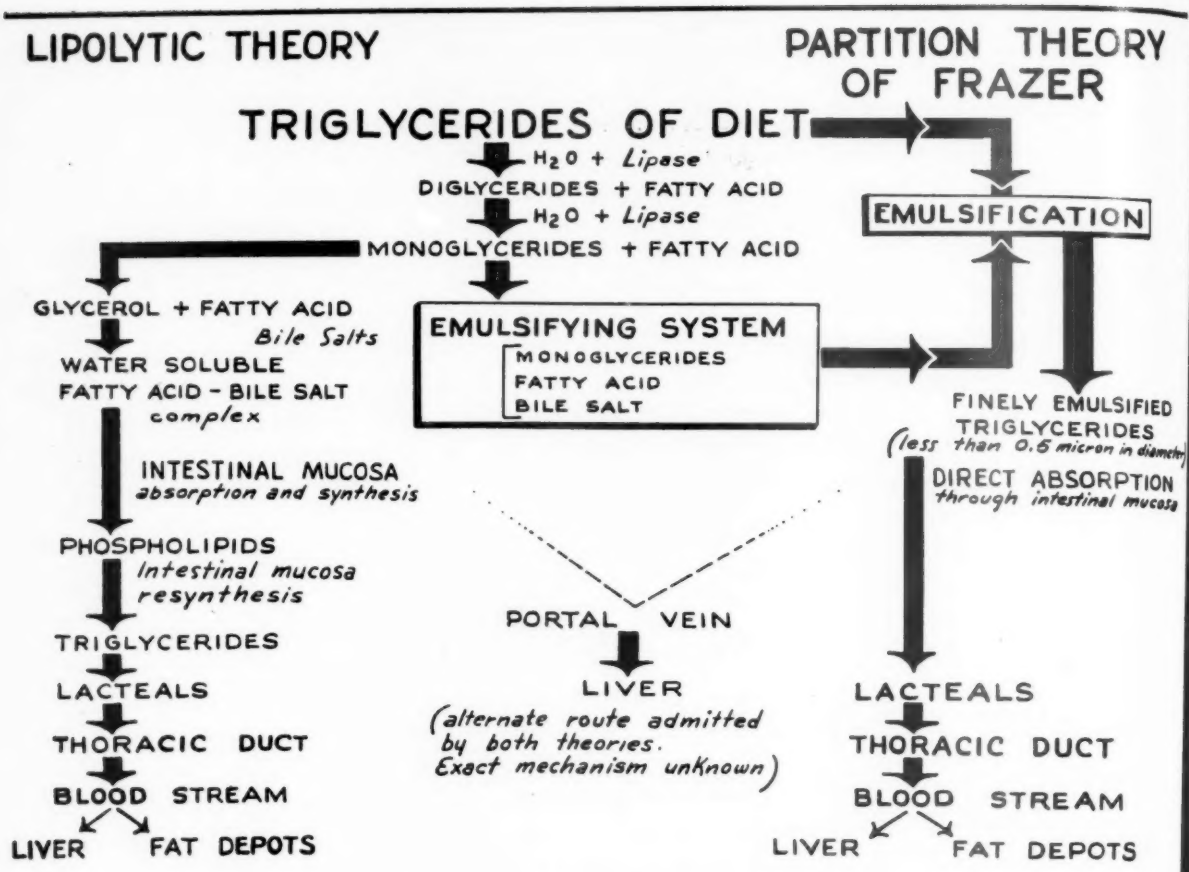
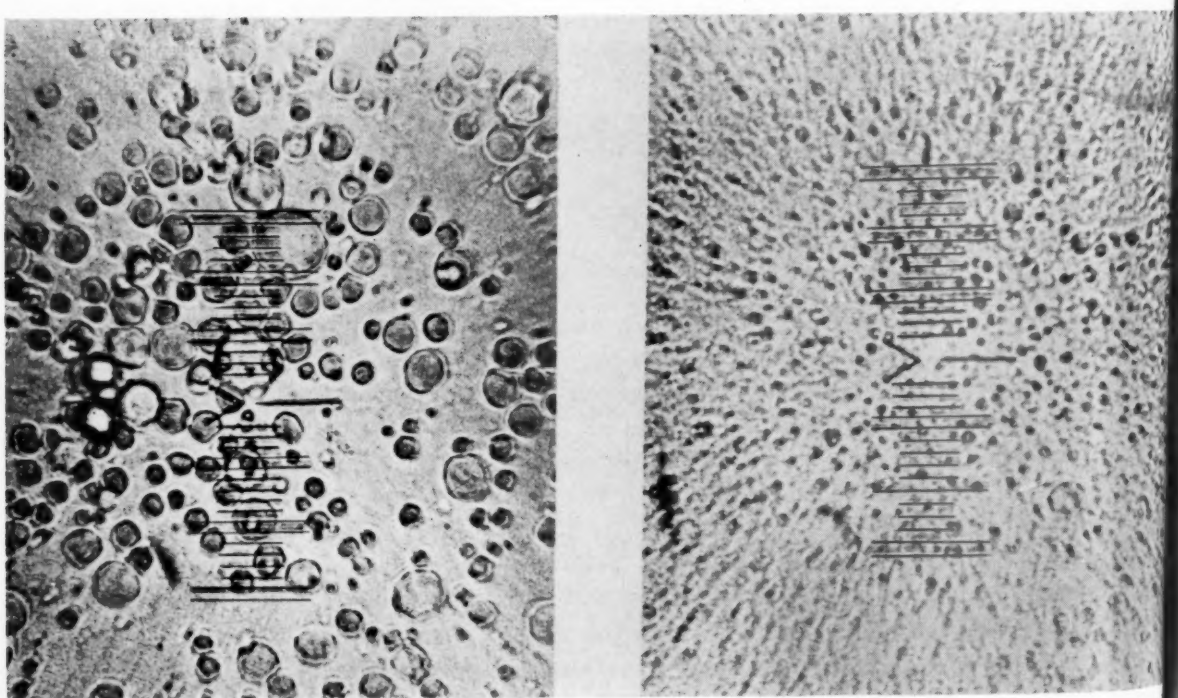


Fig. 1.—Theories of fat absorption. (All illustrations prepared by Mr. Gabriel Evancy, medical illustrator, Department of Surgery, Ohio State University.)



A. *B.*

Fig. 2.—Size of fat globules in milk. *A*, Ordinary milk; *B*, homogenized milk. Each of the small scale divisions represents 2 micra. (Magnification ×950.)

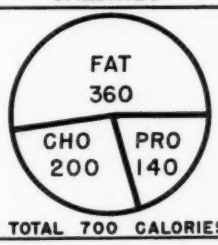
While Frazer did not deny the lipolytic theory in toto, he believed that in addition to this method of fat absorption by complete hydrolysis there is a second possible mechanism: (1) The monoglycerides and fatty acids produced by partial hydrolysis of some of the fat together with the bile salts present in the small intestine form an emulsifying system which reacts with the remainder of the ingested neutral triglycerides to emulsify them into small neutral fat particles less than 0.5 micron in diameter; (2) these finely emulsified particles of neutral fat are then absorbed directly through the intestinal mucosal cells in unchanged form and pass either directly into the lacteals or into the blood stream leading to the liver. Frazer called this absorption of finely emulsified neutral fat particles *the partition theory of fat absorption.*

If the absorption of fat according to the partition theory does occur in the body, it was postulated that perhaps the tolerance of the jejunum to milk fat could be increased by decreasing the particle size of the fat globules in milk. Fat particles in normal milk vary from 1 to 18 micra in size with an average of 4 micra, while homogenized milk fat particles range from 0.5 to 2 micra in diameter with an average of 0.76 micra.[16] This difference in particle size is well shown in Fig. 2.

HOMOGENIZED MILK

(PER LITER)

CONSTITUENTS	GRAMS	CALORIES
FAT (FINELY DIVIDED PARTICLES)	40	
CARBOHYDRATE	50	
PROTEIN	35	



TOTAL 700 CALORIES

SUGGESTED DAILY TOTAL VOLUME

2400 cc { 84 GRAMS PROTEIN
TOTAL 1680 CALORIES

Fig. 3.

The next step of the investigation was to try commercially prepared undiluted homogenized milk on dogs with Mann-Bollman jejunostomies[17] and on patients with Stamm jejunostomies.[3, 5] In contrast to regular whole milk which had not been tolerated, *homogenized milk was tolerated regularly by both the dogs and the patients within twenty-four hours of the construction of the jejunostomy.* In addition to possessing all the previously mentioned advantages of whole milk and also of having small fat particles, homogenized milk provides per liter 700 calories and 35 Gm. of protein in a single solution (Fig. 3), while Scott and Ivy's pabulum[9] with its thirteen constituents provides only 800 calories and 35 Gm. of protein per liter. Vi-Syneral*

*Vi-Syneral was kindly provided by its manufacturers, the United States Vitamin Corporation, New York, N. Y.

Vi-Syneral, 0.6 c.c. contains vitamin A., 5000 U. S. P. units; vitamin D, 1000 U. S. P. units; ascorbic acid, 50 mg.; thiamine, 1 mg.; riboflavin, .4 mg.; pyridoxine, .1 mg.; niacinamide, 5 mg.; pantothenic acid, 2 mg.

(selected because it is water soluble and seems to mix the best with milk of the vitamin preparations tried), 0.6 c.c. is added to each liter of homogenized milk. This combination provides the standard vitamins in excess of the minimum daily requirements of each.

After many trials, the following method of administration was developed and has proved to be well tolerated by a number of patients (Fig. 4):

1. Six hours after its construction, feedings of 5 per cent dextrose in normal saline solution are begun by gravity drip[18] into the jejunostomy at a rate of 50 c.c. per hour. No ill effects have followed such an early utilization of the jejunostomy, which may be of theoretical value in preparing the jejunum for the more concentrated feedings to follow. Early distention of the jejunum likewise appears to stimulate intestinal motility, and may thereby lessen the number of adhesions.[19]

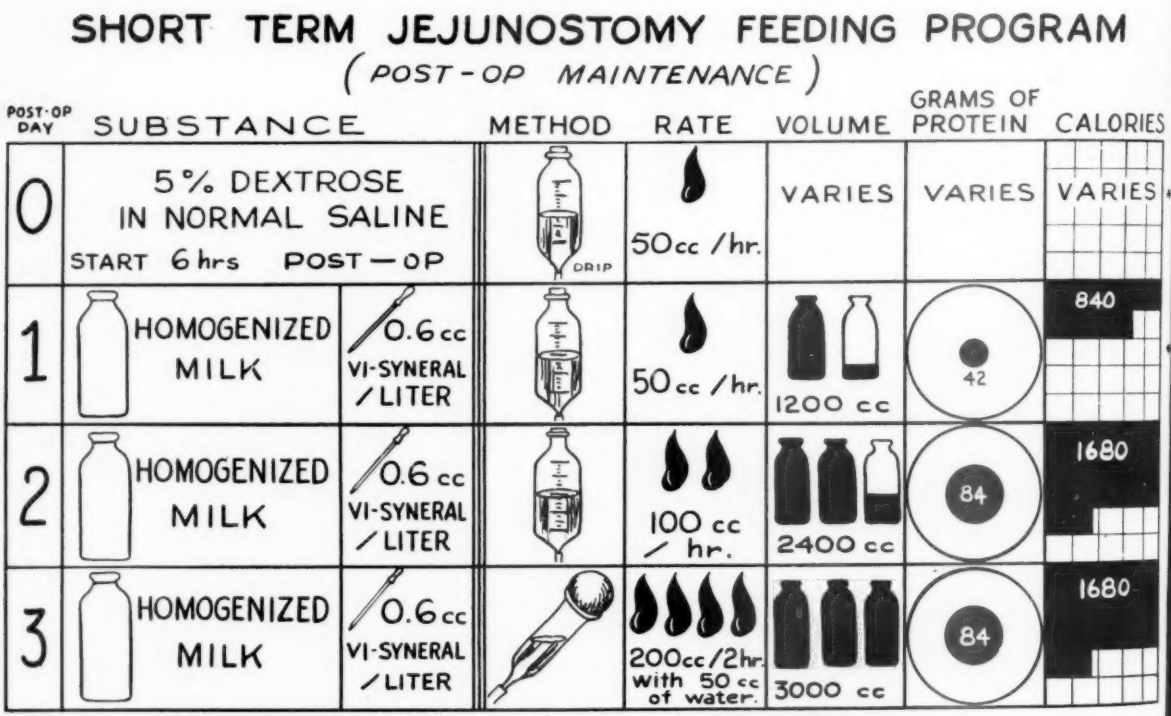


Fig. 4.

2. Starting at 7 A.M. on the day after operation (first postoperative day), homogenized milk is given into the jejunostomy tube by continuous gravity drip at the rate of 50 c.c. per hour, providing 1,200 c.c. of fluid and 840 calories in twenty-four hours. This may be supplemented, if desired, with 1,000 to 2,000 c.c. of 10 per cent dextrose in distilled water intravenously, the last day that additional fluids are needed.

3. Starting at 7 A.M. on the second postoperative day the administration of homogenized milk is increased to 100 c.c. per hour by gravity drip. This provides 2,400 c.c. of fluid, 1,680 calories, and 84 Gm. of protein daily which is more than adequate to meet the basic fluid, caloric, protein, mineral, and vitamin requirements of the average convalescent patient.

4. On the third postoperative day the gravity drip may be discontinued. The homogenized milk is administered directly by asepto syringe into the jejunostomy tube at the rate of 200 c.c. every two hours with 25 c.c. of water used before and 25 c.c. used after each feeding to wash out the tube and prevent clogging. The daily intake thus remains at 1,680 calories and 84 Gm. of protein, but the fluid intake is increased to 3,000 c.c. For the succeeding days the same regime is followed.

Feedings must not be pushed too rapidly before normal bowel function is resumed. The patient must be observed for evidence of peristalsis or passage of flatus. If the lower colon does not empty within the first two or three days, motility should be aided with an enema, rectal tube, suppository, or mineral oil given through the jejunostomy tube.

This regime starting with the day of operation and increasing gradually as outlined is designated the short term jejunostomy feeding program. Unsupplemented, this simple regime with homogenized milk and Vi-Syneral will maintain a patient well for a five- to ten-day period. In the vast majority of patients oral feedings can be built up to adequate levels within this period after intestinal anastomoses or other radical surgery.

Certain patients, however, with severe malnutrition or inoperable total obstruction may require jejunostomy feedings for a protracted period. Further investigations were carried out to determine suitable mixtures with greater caloric and protein content for restoring and maintaining nutritional balance in such patients. The initial aim was to increase calories without proportionately raising the volume or changing the osmotic concentration and reaction of the mixture. The addition of fat could accomplish this because it is neutral and osmotically inactive.

Following the partition theory of Frazer it was decided to prepare finely emulsified fat mixtures of increased concentration. To aid in the emulsification recently developed, non-ionic surface active agents known as Spans* (long chain fatty acid partial esters of hexitol anhydrides including sorbitans and sorbides, mannitans and mannides) and Tweens* (polyoxyalkylene derivatives of hexitol anhydride partial long chain fatty acid esters) were used. Spans and Tweens have been shown[20] to increase the utilization of orally ingested fat and to be tolerated by the small intestine in concentrations up to 5 per cent.[21] The various Spans so thickened the milk mixtures by making a water-in-oil emulsion that they would not drip satisfactorily. The Tweens, however, aided in emulsification and stability of the final product. Tween 80 (polyoxyethylene sorbitan monooleate) used in 0.5 per cent concentration proved to be the most satisfactory for the emulsification of mixtures of milk

*Spans and Tweens are products of the Atlas Powder Company, Wilmington, Del., and were kindly provided by them.

and butterfat, or corn oil and water. A one-stage dairy homogenizer with 3,500 pounds pressure was used to break up the fat particles. Mixtures employing Tween 80 in 0.5 per cent concentration were passed through the homogenizer, resulting in emulsions whose fat particles averaged less than 1 micron in diameter as measured by a micrometer under a microscope. Of the particles, 95 per cent were less than 2 micra in diameter. Various concentrations of butterfat in milk (up to 12 per cent) and corn oil in water (up to 12 per cent) were thus treated and made available for feeding.

The dogs with Mann-Bollman jejunostomies tolerated the 12 per cent fat mixtures of either milk and cream, or corn oil and water without diarrhea or discomfort. The patients with Stamm jejunostomies tolerated up to 8 per cent fat mixtures. Further investigations are being conducted to find the optimum fat concentration of milk and cream mixtures that will result in the best utilization of calories ingested by the body.

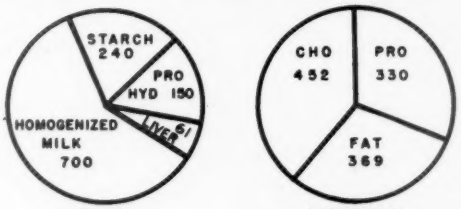
It was felt that the patients with severe nutritional deficiencies would profit by increasing the protein and carbohydrate components of the feeding mixture in addition to the fat component. It was observed that jejunostomy patients would tolerate a mixture of 10 per cent protein hydrolysate in water, or a mixture of 10 per cent starch hydrolysate in water. However, when either the 10 per cent protein hydrolysate mixture or the 10 per cent starch hydrolysate mixture was added to the previously tolerated 8 per cent emulsified, homogenized fat in milk mixture, the patients generally developed abdominal cramps and diarrhea. When all three components were mixed together and given, the patients always developed severe diarrhea, even if jejunostomy had been present for a considerable time. There was the further difficulty that in the preparation of the mixtures the added protein hydrolysate frequently broke the fat emulsions by its salting out effect and change in the pH. Only when the fat-in-milk emulsions were allowed to cool thoroughly before adding the protein hydrolysate or starch hydrolysate would the emulsions remain stable in the presence of added material. The difficulties encountered in preparing the high caloric mixtures, and the tendency of the mixtures to produce diarrhea, re-emphasized the fact that jejunostomy feedings must not have too high a concentration. The simpler they are, the better they are.

After a series of experiments on dogs and patients employing varying concentrations of fat, protein hydrolysate, and starch hydrolysate, it was found that regular homogenized milk with only 4 per cent fat to which was added 50 Gm. of protein hydrolysate per liter and 60 Gm. of starch hydrolysate per liter produced the highest concentration that the jejunum would tolerate regularly. This mixture was called the "4-5-6 mixture" (4 per cent fat in milk, 5 per cent added protein hydrolysate, 6 per cent added starch hydrolysate). There are occasional patients who will not even tolerate this concentration, but the last seven patients have taken it well. To provide adequate amounts of iron and certain indefinite nutritional factors of whole liver, 50 Gm. of puréed liver (pork liver as obtained in cans of baby food) are added to each liter of the mixture. This final mixture is called the long-term jejunostomy feeding mixture and contains 1,151 calories per 1,100 c.c. (Fig. 5).

LONG TERM JEJUNOSTOMY FEEDING MIXTURE

(PER 1100 cc)

COMPONENTS	AMOUNT
HOMOGENIZED MILK	1000 cc
PROTEIN HYDROLYSATE	50 GMS.
STARCH HYDROLYSATE	60 GMS.
PUREED LIVER	50 GMS.
VI SYNERAL	0.6 cc



CALORIES

TOTAL 1151 / 1100 cc.

SUGGESTED DAILY TOTAL VOLUME

2400 cc { 180 GMS. PROTEIN
2500 CALORIES

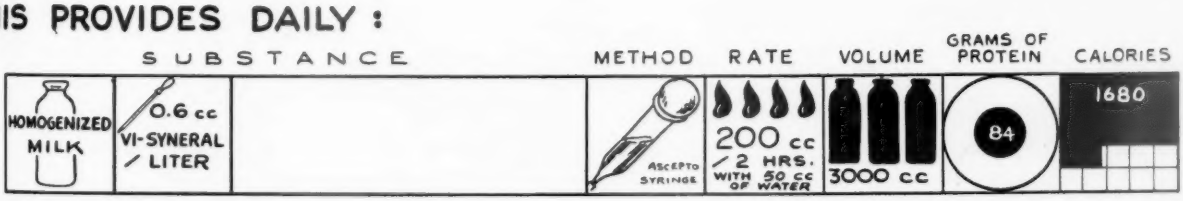
Fig. 5.

LONG TERM JEJUNOSTOMY FEEDING PROGRAM

(NUTRITIONAL RESTORATION)

BEGIN AND BUILD UP FEEDING WITH HOMOGENIZED MILK AS IN SHORT TERM FEEDING PROGRAM FOR 5 to 9 DAYS TILL INTESTINAL FUNCTION IS NORMAL.

THIS PROVIDES DAILY :



THEN FOR 2 DAYS :

IF WELL TOLERATED, INCREASE TO FINAL MIXTURE :

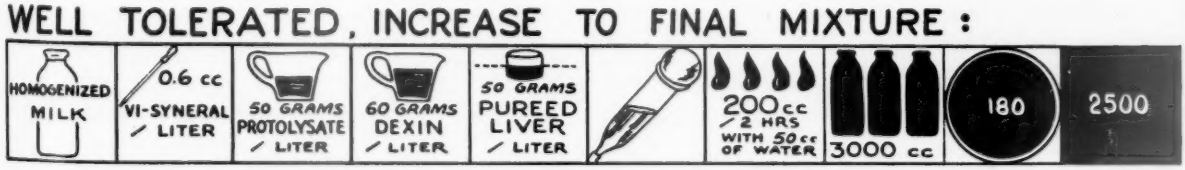

HOMOGENIZED MILK
0.6 cc VI-SYNERAL / LITER
50 GRAMS PROTOLYSATE / LITER
60 GRAMS DEXIN / LITER
50 GRAMS PUREED LIVER / LITER
200 cc / 2 HRS WITH 50 cc OF WATER
3000 cc
180
2500

Fig. 6.

The long-term jejunostomy feeding program for nutritional restoration of severe deficiencies over a long period of time is as follows (Fig. 6):

1. Homogenized milk is begun and gradually increased exactly as outlined previously in the short-term feeding program. The patient is maintained on this regime for five to nine days.

2. When the patient is tolerating these feedings well with full return of normal intestinal motility and evacuation, to each liter of homogenized milk is added 50 Gm. of Protolysate* or of Protogest,† and 30 Gm. of Dexin‡ (a starch hydrolysate which contains 75 per cent dextrins and 25 per cent maltose). Added carbohydrate is preferred in the form of dextrins rather than simple sugars because of the smaller increase produced in total osmotic concentration.[10] Protolysate or Protogest, 50 Gm., provides 37.5 Gm. of additional protein. The patient is fed 200 c.c. of this mixture every two hours by asepto syringe directly into the jejunostomy tube with 25 c.c. of water before and after each feeding. This provides 3,000 c.c. of fluid, 2,100 calories, and 160 Gm. of protein daily.

3. If the mixture outlined in the second step is well tolerated for two days, the amount of Dexin is increased to 60 Gm. per liter, the Protolysate or Protogest is maintained at 50 Gm. per liter, and 50 Gm. of puréed liver are added per liter giving 1,151 calories with 82.5 Gm. of protein in each 1,100 c.c. of the final mixture. This is fed at the same rate of 200 c.c. every two hours by asepto syringe with 25 c.c. of water before and after each feeding to provide 3,000 c.c. of fluid with over 2,500 calories and 180 Gm. of protein intake daily.

This long-term jejunostomy feeding is more complicated, more difficult to prepare, and more prone to produce unwelcome symptoms than the simple short-term feeding mixture. The long-term mixture is to be reserved for the severely depleted patient only.

The Stamm type of jejunostomy has proved to be the simplest and best. Obstruction may occasionally follow the infolding carried out with the Witzel type jejunostomy, and hence has been abandoned in this clinic. The jejunostomy opening will close spontaneously with little drainage within forty-eight hours after removal of the tube.

SUMMARY AND CONCLUSIONS

1. Commercially prepared homogenized milk is a widely available, economical, almost complete food substance. In contrast to whole milk, it is well tolerated by the jejunum from the first day after construction of a jejunostomy, probably due to the smaller size of the fat particles.

2. Sufficient amounts of homogenized milk can be given from the second day after construction of a jejunostomy to provide the basic fluid, caloric, protein, vitamin, and mineral requirements of the patient of average size.

*Protolysate, brand of protein hydrolysate prepared and provided by Mead Johnson & Company, Evansville, Ind.

†Protogest, brand of protein hydrolysate prepared and provided by Burroughs Wellcome & Co., Inc., New York, N. Y.

‡Dexin, brand of starch hydrolysate prepared and provided by Burroughs Wellcome & Co., Inc., New York, N. Y.

3. Concentrations of 8 per cent homogenized fat in milk, 10 per cent protein hydrolysate in water, or 10 per cent strach hydrolysate in water can be tolerated individually by the jejunum, but they are not tolerated in combination. However, 4 per cent homogenized fat in milk (the concentration in commercial homogenized milk) enriched with protein hydrolysate up to 5 per cent and starch hydrolysate up to 6 per cent, the so-called 4-5-6 mixture, appears to be well tolerated by the jejunum.

4. For the severely malnourished patient the 4-5-6 mixture to which is added 50 Gm. of puréed liver per liter will hasten nutritional restoration. This mixture should not be given by jejunostomy until homogenized milk in amounts of 2,400 c.c. per twenty-four hours has been well tolerated for one week to ten days.

5. Details of short-term and long-term simplified jejunostomy feeding programs are given.

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THE INFLUENCE OF CALORIC INTAKE UPON THE FATE OF PARENTERAL NITROGEN

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THE widespread appreciation of the importance of nutrition, with particular reference to protein, has played a significant role in lowering morbidity and mortality in the surgery of poor-risk patients. There is general agreement that the most effective method of nutritional therapy is by way of the gastrointestinal tract.[1, 2] In many instances, however, the only practical method of alimentation is by the intravenous route. As a result, there is increasing utilization of the various protein products which may be given intravenously.[3-7]

The strong emphasis placed on meeting protein requirements has resulted in a tendency to overlook the importance of supplying a sufficient number of calories to meet basal energy requirements. If not met, the infused protein is burned as a source of energy and thus lost for tissue synthesis.[8] Should the caloric deficit be very great, there may even be a raiding of tissue protein for energy needs.[9] There has been considerable confusion as to what constitutes an optimal caloric intake. Figures varying from 6 to 45 calories per kilogram per day are to be found in the literature. The disagreement is more apparent than real and depends primarily on whether the desired end is protein maintenance or protein restoration (Fig. I).

Elman[10] has introduced the concept of "minimal" protein maintenance. "Minimal," defined as that caloric intake sufficient to prevent ketosis and tissue protein breakdown, was found by him to be 6 calories per kilogram, or 100 grams of glucose per day for the adult weighing an average of 70 kilograms. Experimental observations[11] have suggested that the remaining energy requirement is supplied by catabolism of dispensable body fat. This applies only to normal individuals over short periods of time.

"Basal" maintenance implies protein conservation without expense to other body tissue. Butler and Talbot[12] have recommended 25 calories per kilogram of body weight per day as the basal requirement for parenteral maintenance in adult individuals at rest in bed. Lund and Levenson,[13] Ravdin,[14] Stare and Thorn[15] and others[2, 12] have repeatedly pointed out that 30 to 45 calories per kilogram are necessary in order to realize any degree of protein restitution and weight gain. Dextrose solutions of 15 and even 20 per cent have been advocated to supply this energy requirement.

Nevertheless, one sees widespread use of 2 or 3 liters of protolysate containing 5 per cent dextrose per day, with the belief that such a regimen will ensure nutritional restitution. It has been the purpose of the present study

Aided in part by a grant from the Mead Johnson & Company, Evansville, Ind.

Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 24-26, 1949.

to determine what constitutes the optimal caloric intake and, by implication, the concentration of glucose which ensures the most efficient utilization of parenteral protein, supplied as a protein hydrolysate (Amigen*). The method employed has been carefully controlled nitrogen balance studies on human subjects.

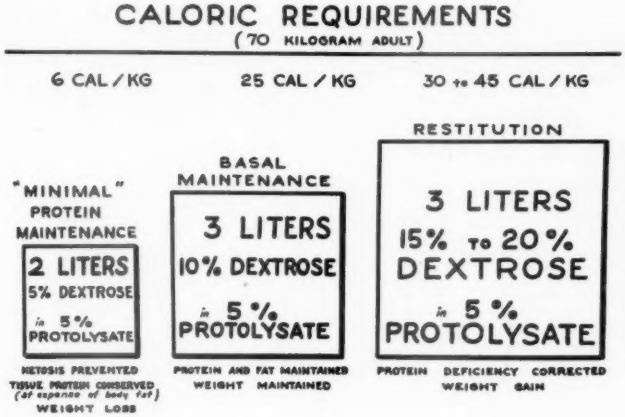

FIG. 1

GENERAL METHODS AND MATERIALS

A separate unit for metabolic studies was designed. This unit was staffed by special personnel whose only duties were those associated with the problem. These included a graduate dietitian, a laboratory technician, and special nurses over each twenty-four hour period. All infusions were administered by a single member of the surgical staff so as to eliminate variations in technique. All foods were accurately measured and their nitrogen content calculated from standard reference tables and checked by sample analysis of the entire daily diet. Twenty-four hour collections of urine, stools, and other discharges were made and their nitrogen content determined. Samples of the parenteral solutions were analyzed for nitrogen. Stool collection periods were marked by enteric-coated capsules of indigo-carmine given on the first day of each period. Urine specimens were preserved by a single crystal of thymol. Food and stool specimens were preserved with concentrated sulfuric acid, homogenized in a Waring Blendor, diluted to 1,000 c.c., and a sample taken for analysis. All specimens were refrigerated in closed containers from the time of collection until final analysis. The nitrogen content in each instance was determined by the standard macro-Kjeldahl procedure.

The twenty-four hour urine specimens were tested for sugar qualitatively; if sugar was present, the exact amount was measured. Hematocrit levels, total serum protein, and serum albumin and serum globulin values were determined at the beginning and end of each experiment. All laboratory analyses were made in duplicate.

The subjects were weighed daily under uniform conditions on a special scale. Local and systemic reactions to the intravenous solutions were carefully

*Supplied by Warren M. Cox, Jr., Ph.D., Director of Department of Nutritional Reseach, Mead Johnson & Company.

noted. An attempt was made to appraise objectively the effect of various levels of parenteral alimentation upon the appetite and to estimate strength and well-being of the patient.

The subjects were protein-impoverished emaciated individuals with lesions in or closely associated with the gastrointestinal tract amenable to surgical correction. A history of inadequate food intake, a 15 to 20 per cent loss of total body weight, and subnormal serum proteins were common to all. This selection was deliberate so that the results might apply directly to the type of patient for whom protein hydrolysate therapy is usually indicated.

The fluid, electrolyte, and acid-base balances were restored to as near normal as possible. Intravenous injections were given by preference in the wrist or forearm. The use of the cubital veins was avoided. Minimal splinting permitted movement of the shoulder and elbow without displacement of the needle. Small needles were used to avoid occlusion of the vein by the needle and to permit a constant flow of blood past the point of injection. Prolonged use of a single vein was avoided by dividing the daily infusions into two or three periods. The rate of injection was controlled by a gravity drip apparatus.

PLAN OF STUDY

PERIOD	DAYS	FEEDING PROGRAM			CALORIES PER DAY	PROTEIN PER DAY
		ORAL	INTRAVENOUS			
			VOLUME PER DAY	SOLUTION		
DEPLETION	7	* PROTEIN FREE DIET ADEQUATE CALORIES			40 CAL./KG	(GMS) 0
I	3	NO ORAL DIETARY INTAKE	3 LITERS	5% DEXTROSE in 5% AMIGEN	1155	113
DEPLETION	2	*			40 CAL./KG	0
II	3	NO ORAL DIETARY INTAKE	3 LITERS	10% DEXTROSE in 5% AMIGEN	1755	113
DEPLETION	2	*			40 CAL./KG	0
III	3	NO ORAL DIETARY INTAKE	3 LITERS	15% DEXTROSE in 5% AMIGEN	2385	113
DEPLETION	2	*			40 CAL./KG	0

FIG. II

PLAN OF STUDY

The stabilization of an individual, insofar as nitrogen exchange is concerned, is best effected when the nitrogen intake approaches zero. Accordingly, the minimum endogenous level of nitrogen excretion was established by means of a seven-day depletion period (Fig. II). The depletion diet, similar to that of Mueller, Fickas, and Cox,[16] consisted chiefly of carbohydrate and supplied a caloric intake of 40 calories per kilogram of body weight per day. The total oral nitrogen intake per day averaged 1.2 grams, the latter composed chiefly of the incomplete protein of fruits and vegetables. For purposes of simplicity, the variety of foods was of necessity small. As unused food makes for considerable error, it was necessary to stay within limits imposed by the desires of the patient. Balance studies were not started until a well-tolerated diet was found.

Following stabilization, a comparison of nitrogen equilibrium was made during three three-day periods of supplementation, as the daily caloric intake was elevated from 1,155 to 1,755 and 2,385 calories. The supplements in each instance consisted of 5, 10, and 15 per cent dextrose in 5 per cent Amigen. The experimental periods involved intravenous alimentation without any oral dietary intake. The periods of supplementation were alternated with two-day depletion periods to avoid the effects of one experimental period blending with those of the succeeding period. Under such an arrangement, each subject served as his own control. Periods of bed rest were required during depletions equivalent to the time necessary for the infusions during supplementation. The total fluid intake was maintained at a constant level. Adequate vitamin B complex and Vitamin C were given daily.

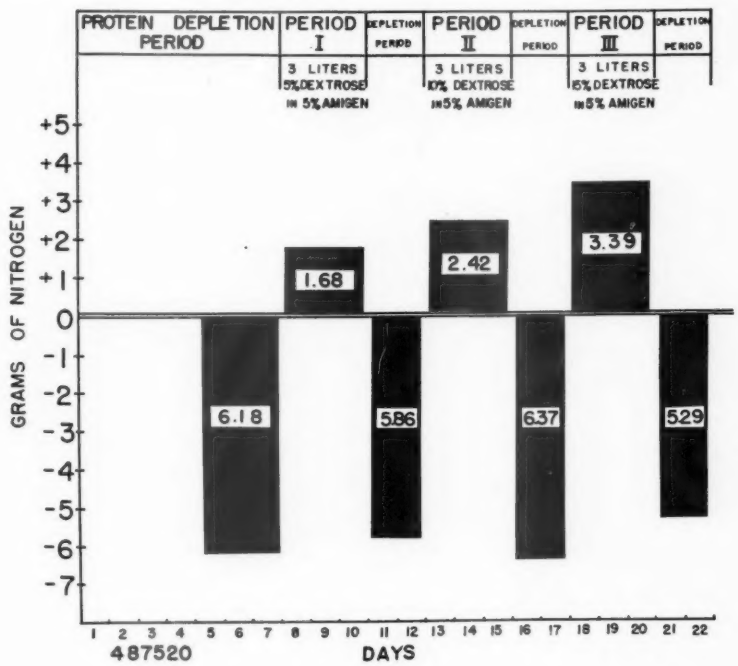

FIG. III

DISCUSSION OF RESULTS

A graphic presentation of the average nitrogen balance of a representative patient is shown in Fig. III. The patient, already protein depleted, arrived promptly at a steady state of nitrogen loss while receiving adequate calories but no protein. The consistent values during the four depletion periods indicate stability of nitrogen metabolism and the suitability of the subject for comparative study. A comparison of individual nitrogen balances (Table I) shows very uniform values, with none of the variations sufficiently large to affect the interpretation.

The phenomenon of "nitrogen lag," an initial large nitrogen retention due to changing a nearly zero nitrogen intake to one of a higher level, is manifest at the beginning of each supplemental period. This change from one

TABLE I. INFLUENCE OF CALORIC INTAKE UPON NITROGEN BALANCE AT A HIGH LEVEL OF PARENTERAL PROTEIN ALIMENTATION
(CASE 1—M. S., 63 YEARS OF AGE, CARCINOMA OF RECTO-SIGMOID)

			NITROGEN						FLUID					
			INTAKE		EXCRETION	BALANCE								
	PERIOD	DAY	ORAL (GM.)	I.V. (GM.)	URINE, STOOL (GM.)	PER DAY (GM.)	PER PERIOD (GM.)	ACCUMULATIVE (GM.)	INTAKE (C.C.)	OUTPUT (C.C.)	BALANCE (C.C.)	URINARY GLUCOSE (GM.)	CALORIES PER DAY (PER KG.)	WEIGHT (POUNDS)
	Depletion	1	1.120											143
		2	1.120											143
		3	1.120										27.9	142¾
		4	1.120											142½
		5	1.120		8.119	−6.999			2,950	1,460	+1,490	0		142½
		6	1.120		7.078	−5.585	−6.187	−18.562	3,000	2,320	+1,680	0		141½
		7	1.120		6.825	−5.705			3,740	3,130	+ 610	0		141
I	3,000 c.c. 5%	8	0	17.280	12.222	+5.058			4,600	3,120	+1,480	Trace		141
	dextrose in 5%	9	0	16.590	12.247	+4.343	+1.680	+ 5.042	3,750	2,675	+1,075	0	216.3	140
	Amigen	10	0	17.140	21.499	−4.359			3,750	2,695	+1,055	0		139
	Depletion	11	1.120	0	7.403	−6.283	−5.861	−11.723	2,650	1,990	+ 660	0	27.9	140
		12	1.120	0	6.560	−5.440			3,100	2,270	+ 820	0		140½
II	3,000 c.c. 10%	13	0	14.760	9.612	+5.148			4,050	2,950	+1,100	0		140½
	dextrose in 5%	14	0	14.810	13.344	+1.466	+2.422	+ 7.267	4,000	3,200	+ 800	Trace	27.1	140½
	Amigen	15	0	15.040	14.387	+ .653			3,400	2,255	+1,145	0		140¾
	Depletion	16	1.510	0	7.206	−5.696	−6.379	−12.758	2,750	1,530	+1,220	0	27.9	140½
		17	1.510	0	7.572	−6.062			2,970	2,340	+ 630	0		142½
III	3,000 c.c. 15%	18	0	15.150	10.552	+4.598			4,025	2,500	+1,525	0		142¾
	dextrose in 5%	19	0	14.810	10.574	+4.236	+3.393	+10.179	3,850	2,380	+1,470	0	36.8	142
	Amigen	20	0	15.170	13.785	+1.345			3,600	2,220	+1,380	0		142¾
	Depletion	21	1.510	0	6.522	−5.012	−5.304	−10.612	2,980	2,000	+ 980	0	27.9	143
		22	1.510	0	7.110	−5.600			3,150	2,280	+ 870	0		143½

level of nitrogen nourishment to another always requires a varying period of adjustment. It follows that if the initial "bump" after supplementation is equal in all three experimental periods, the subsequent daily nitrogen balance and the average for each of the three-day periods should be different if the higher caloric intake is accomplishing some degree of nitrogen spring. One can see by inspection that the initial degrees of nitrogen retention following supplementation are nearly identical. A study of subsequent daily balances and, in particular, the average values (see Fig. III) for nitrogen retention during Periods I, II, and III clearly demonstrates an increased retention of protein nitrogen as the daily caloric intake was elevated by the use of 5, 10, and 15 per cent dextrose in Amigen. The effect was not cumulative, as evidenced by the consistently negative balance of intervening depletion periods.

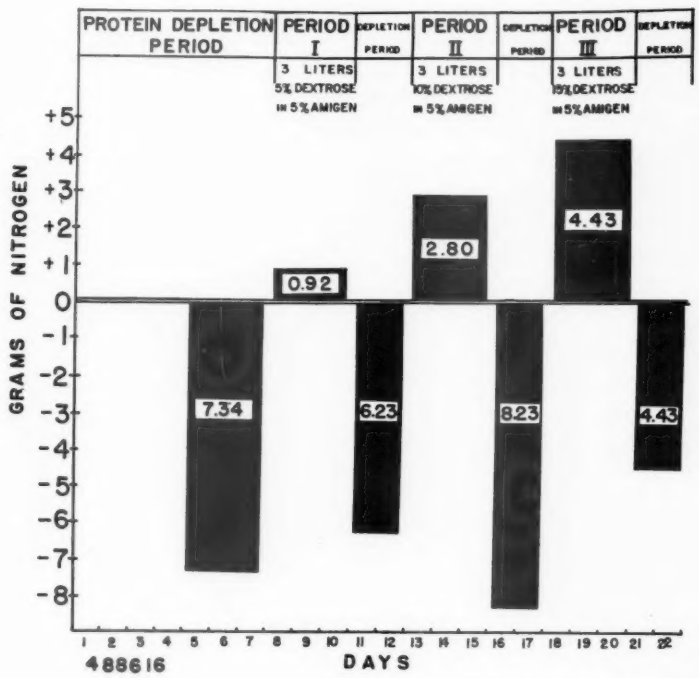

FIG. IV

The protein intake remained constant during the experimental periods at 113 grams per day, being supplied in each instance by 3 liters of 5 per cent Amigen. The one variable, that of increased glucose concentrations, or, in other words, increased caloric intake, would seem to be the only explanation for the increased nitrogen retention. These findings agree with those of Cannon,[17] who found in his work with dogs and rats that if adequate protein is assured, tissue synthesis proceeds in a direct relation to the calories supplied.

In another representative patient (Case 2, Table II, Fig. IV) handled in an identical manner to the first patient, the relationship between caloric intake and nitrogen retention is even more strikingly demonstrated. A positive

TABLE II. INFLUENCE OF CALORIC INTAKE UPON NITROGEN BALANCE AT A HIGH LEVEL OF PARENTERAL PROTEIN ALIMENTATION
(CASE 2—J. E., 57 YEARS OF AGE, GASTRIC CARCINOMA)

PERIOD	DAY	NITROGEN						FLUID			URINARY GLUCOSE (GM.)	CALORIES PER DAY (PER KG.)	WEIGHT (POUNDS)
		INTAKE		EXCRETION	BALANCE								
		ORAL (GM.)	I.V. (GM.)	URINE, STOOL (GM.)	PER DAY (GM.)	PER PERIOD (GM.)	ACCUMULATIVE (GM.)	INTAKE (C.C.)	OUTPUT (C.C.)	BALANCE (C.C.)			
Depletion	1	1.68										34.1	118¼
	2	1.68										34.1	117
	3	1.68										34.1	116
	4	1.68		10.922	−9.242			3,300	2,770	+ 730	0	34.1	115
	5	1.68		8.420	−6.740	−7.340	−22.022	3,600	2,800	+ 800	0	34.1	115½
	6	1.68		7.720	−6.040			3,900	3,300	+ 600	0	34.1	115
I 3,000 c.c. 5%	7	0	16.950	14.420	+2.530			4,000	3,500	+ 500	0		113½
dextrose in 5%	8	0	16.650	12.695	+3.955	+ .920	+ 2.760	4,300	2,730	+1,570	0	21.6	114¼
Amigen	9	0	15.270	18.995	−3.725			4,250	2,620	+1,630	0		115
Depletion	10	1.34	0	8.397	−7.057	−6.236	−12.437	4,250	2,820	+1,430	0	33.4	116½
	11	1.34	0	6.756	−5.416			3,800	3,010	+ 790	0		116¼
II 3,000 c.c. 10%	12	0	14.950	11.469	+3.481			4,700	3,830	+ 780	0		115¾
dextrose in 5%	13	0	15.109	10.128	+4.981	+2.803	+ 8.419	4,800	3,010	+1,790	10.2	32.5	117
Amigen	14	0	15.287	15.330	−0.043			3,900	2,540	+1,360	16.7		118
Depletion	15	1.28	0	10.389	−9.109	−8.226	−16.452	3,700	2,300	+1,400	0	33.4	119¼
	16	1.28	0	8.623	−7.343			3,850	3,250	+ 600	0		117½
III 3,000 c.c. 15%	17	0	15.007	9.993	+5.010			3,900	3,630	+ 270	36.3		116½
dextrose in 5%	18	0	14.883	8.226	+6.657	+4.429	+13.287	4,200	3,690	+ 510	62.7	41.5	115½
Amigen	19	0	14.917	13.297	+1.620			3,800	2,250	+ 550	45.0		115¾
Depletion	20	1.28	0	1.548	−0.268	−4.476	− 8.956	3,400	865?	+2,535	0	33.4	117½
	21	1.28	0	10.964	−8.684			3,550	2,270	+1,128	0		117¾

balance three times as great was obtained with 10 per cent concentrations of dextrose as compared with the 5 per cent and twice as great with the concentration of 15 per cent dextrose as compared with 10 per cent. Body weight increased steadily during supplementation. Supported by the fact that the hematocrit levels were the same or slightly higher at the completion of the experiment as compared to the base lines, this weight gain probably represents tissue replacement rather than water retention. This, coupled with the staircase effect on nitrogen retention, implies a more efficient utilization of protein at the higher levels of caloric intake.

PLAN OF STUDY

PERIOD	DAYS	FEEDING PROGRAM ORAL	INTRAVENOUS VOLUME PER DAY	INTRAVENOUS SOLUTION	CALORIES PER DAY	PROTEIN PER DAY
DEPLETION	9	PROTEIN FREE DIET ADEQUATE CALORIES			40 CAL/KG	(GMS) 0
I	8	NO ORAL DIETARY INTAKE	2 LITERS	10% DEXTROSE in 5% AMIGEN	1170 or 23 CAL / KG	75
II	8	NO ORAL DIETARY INTAKE	3 LITERS	10% DEXTROSE in 5% AMIGEN	1755 or 35 CAL / KG	113

FIG. V

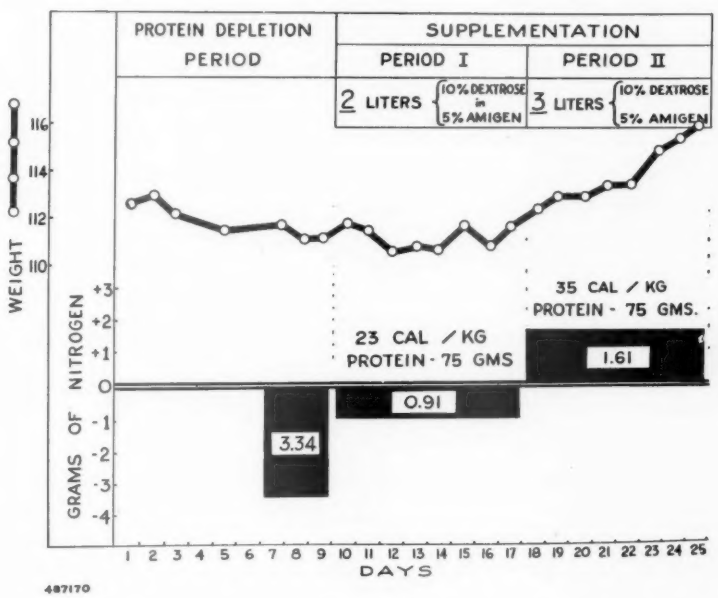

FIG. VI

The usual precautions recommended for administration of hypertonic glucose solutions proved satisfactory. Local reactions were minimal, both as to degree and number. By maintaining the rates of infusion so that the ratio of glucose administration did not exceed .6 grams of glucose per kilogram

per hour, glycosuria and diuresis were avoided. This corroborates the recent work of Lockhart and Elman.[18]

It would seem, therefore, that with no greater effort on the part of the clinician, or added discomfort to the patient, it is possible to double the efficiency of protein utilization without increasing protein intake.

Is it possible to arrange by simple calculations "basal" and "restitution" regimens for any given patient? Further balance studies were devised to answer this question.

The plan of study in one instance is shown in Fig. V. The observations represent complete metabolic studies of twenty-five days' duration. Stabilization was accomplished in a nine-day depletion period. This was followed by two eight-day periods of supplementation, representing exclusive parenteral feeding for sixteen days. The 75 grams of protein and 23 calories per kilogram of Period I, supplied by 2 liters of 10 per cent dextrose in 5 per cent Amigen, corresponds to values accepted for maintenance. During period II, the level of parenteral nourishment was increased to 113 grams of protein and 35 calories per kilogram, which should result in some degree of restoration. The average nitrogen balance for each period is shown in Fig. VI. During Period I, nitrogen equilibrium was not quite attained at calculated maintenance levels; however, weight was maintained. On the other hand, a positive balance was realized during Period II with corresponding weight gain. This again demonstrates that intravenous feedings may be useful even for long periods of time. As measured by the dual criteria of a positive nitrogen balance and weight gain, a patient's nutritional status can be maintained and restitution assured provided sufficient protein and calories are given.

With one exception, the *total serum protein* values were increased in all subjects. The exception, Case 2, actually represented a fall in a high serum globulin. The serum albumin was elevated in each instance.

In several cases in which these experiments preceded extensive abdominal surgery, the patients underwent operation without difficulty and convalesced rapidly without complications.

CONCLUSIONS

1. The utilization of protein given intravenously is related to the total calories administered simultaneously.

2. Even though nitrogen intake remains constant, nitrogen retention is increased when total calories are increased.

3. In practice, the higher concentrations of glucose are preferable to the commonly employed 5 per cent glucose in 5 per cent protolysate.

4. The choice between 10 and 15 per cent concentrations of glucose and the total daily amounts of 5 per cent protolysate to be administered to any given patient will depend upon the goal of the clinician. For example, an adult weighing an average of 70 kilograms will require 2 liters of 15 per cent dextrose or 3 liters of 10 per cent dextrose in 5 per cent protolysate per day for "basal" maintenance. The same patient will require 3 liters of 15 per cent dextrose in 5 per cent protolysate per day to assure restitution of protein and weight gain.

Grateful acknowledgment is given to Warren M. Cox, Jr., Ph.D., Director, Department of Nutritional Research, Mead Johnson & Company, for helpful suggestions and technical aid; also to Miss Margorie Brock, Department of Dietetics, Ohio State University, College of Medicine, for the preparation of diets used in these studies.

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PRESCHOOL AGE REPAIR OF HYPOSPADIAS WITH FREE INLAY SKIN GRAFT

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HYPOSPADIAS is a congenital anomaly occurring when ventral closure of the urethral tube does not take place. The urinary meatus may be located from the perineum to the frenulum of the glans penis. In the more severe forms there is an associated ventral bowing of the organ called chordee. The curved, bent penis prevents normal sexual function and the abnormal position of the urinary meatus makes it necessary for the patient to sit down to urinate. Because of the abnormal appearance of the genitals, psychic difficulties at times arise. These range from the troubles of the young boy twitted by his schoolmates because he cannot stand to urinate, to the morbid introspection of the adolescent regarding his deformed sexual apparatus, or to the actual later marital difficulties.

The objectives in correcting this condition are, first, an organ sufficiently straight on erection to allow satisfactory sexual function; second, a satisfactory urinary stream in the standing position; and third, near normal appearance.

It is commonly agreed that correction falls into two distinct procedures: the correction of the chordee, and construction of the missing urethra. However, there is incomplete agreement on the type of operation which best accomplishes the desired result and the age at which the operation is best done. We do not wish to be dogmatic about these matters as have some who state that the urethra should not be reconstructed until the age of 16 years,[20] but we do want to present a detailed analysis of the results obtained, as far as urination is concerned, by the construction of the urethra at an early age with a free inlay skin graft.

In general we believe that hypospadias has been repaired too late in life. The ideal time to repair congenital deformities is in early childhood and hypospadias is no exception. By so doing, unnecessary mental anguish is avoided and the tendency of the deformity to become fixed is prevented. It seems probable that hypospadias repair is often delayed because of the greater ease in operating upon the larger organ of later years. This is particularly true of the various flap type repairs commonly used.

We began the type of repair presented here in 1940. We were dissatisfied with the results obtained by the usual types of chordee repair, the multiple operations necessary in the ordinary flap type of repairs for construction of the urethra, the late age often advised for urethral reconstruction, and the

Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 24-26, 1949.

Aided in part by the Dr. Henry C. Buswell Memorial.

common failure to obtain an intact urethra even after numerous attempts. At that time we reviewed the methods in common use and those advocated in the past with the idea in mind of selecting a principle of repair which could most nearly meet the requirements of providing an adequate repair in few operative steps in early childhood.

HISTORICAL BACKGROUND

It is well recognized that hypospadias is an extremely difficult condition to correct. In an earlier report[45] we noted that the literature on hypospadias was voluminous and that the magnitude of the problem was attested to by the great number of procedures which have appeared in the literature. However, we found, after review of this mass of material, that probably no more than seven different surgical principles had been reported in the past. We also discovered that the great majority of reports deal with some minor modification of technique; reports dealing with an analysis of long-term results are notable exceptions.

Since our earlier report reviewed in detail the principal types of repair previously reported they will be considered only briefly. The types of repair can be divided into two major groups: Flap repair and free graft repair.

Chronologically these are:

A. Construction of urethra with flaps
   1. Dieffenbach, 1837-1845
   2. Thiersch-Duplay, 1869-1874
   3. Rochet, 1899
   4. Bucknall, 1907
   5. Ombrédanne, 1911

B. Construction of urethra with free graft
   1. Nové-Josserand, 1897-1919
   2. Miscellaneous methods, 1909-1927

Briefly these methods are:

A. *Construction of Urethra With Flaps.*—

1. Dieffenbach, 1837-1845.[7] The urethra was reconstructed by folding the ventral skin of the penile shaft into a skin-lined tube which ended at the frenulum. This was covered over by undermining the skin laterally and suturing it in the midline over the skin tube. The two suture lines coincided. If this was successful, an attempt was made to draw the constructed epithelial tube through the glans at a second operation.

2. Thiersch-Duplay, 1869-1874.[42-44, 8-13] This repair involved three surgical steps. First, correction of the chordee by a transverse incision on the ventral shaft of the penis anterior to the meatal orifice. The first segment of the corpus spongiosum was excised. The skin was then closed after the principle of Heineke-Mikulicz. Second, the urethra was constructed from the ventral penis skin. This differed from Dieffenbach's procedure in that the incisions, outlining the ventral skin to be turned inward to line the new urethra, were made so that one ran parallel to and close to the midline and the other was made parallel and considerably lateral to the midline. When the skin was drawn over this turned-in tube, the two suture lines did not coincide. Third, if the tube were successfully made, the old and new urethra were joined.

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3. Rochet, 1899.[40] The urethra was reconstructed with a flap taken from the scrotum with its base at the hypospadias meatus. In this way the temporary fistula between the old and new urethra was eliminated. (A step forward as the Dieffenbach and Thiersch-Duplay procedures both constructed the new urethra and later joined it to the old.) This flap was sewed around a catheter and inserted into a tunnel canal. The urethra ended at the frenulum.

4. Bucknall, 1907.[5] The urethra was constructed of ventral skin of the penis dorsally and of the scrotal skin ventrally. Incisions were made on either side of the midline on the ventral surface of the penis. These were continued downward on either side of the median raphe of the scrotum. The hypospadias meatus was in the center of the rectangle thus outlined. The penile shaft was bent downward on the scrotum and the two flaps sutured together. A catheter was inserted through the newly constructed urethra. In three to four weeks the penis and the new urethra were dissected off the scrotum and the skin edges closed.

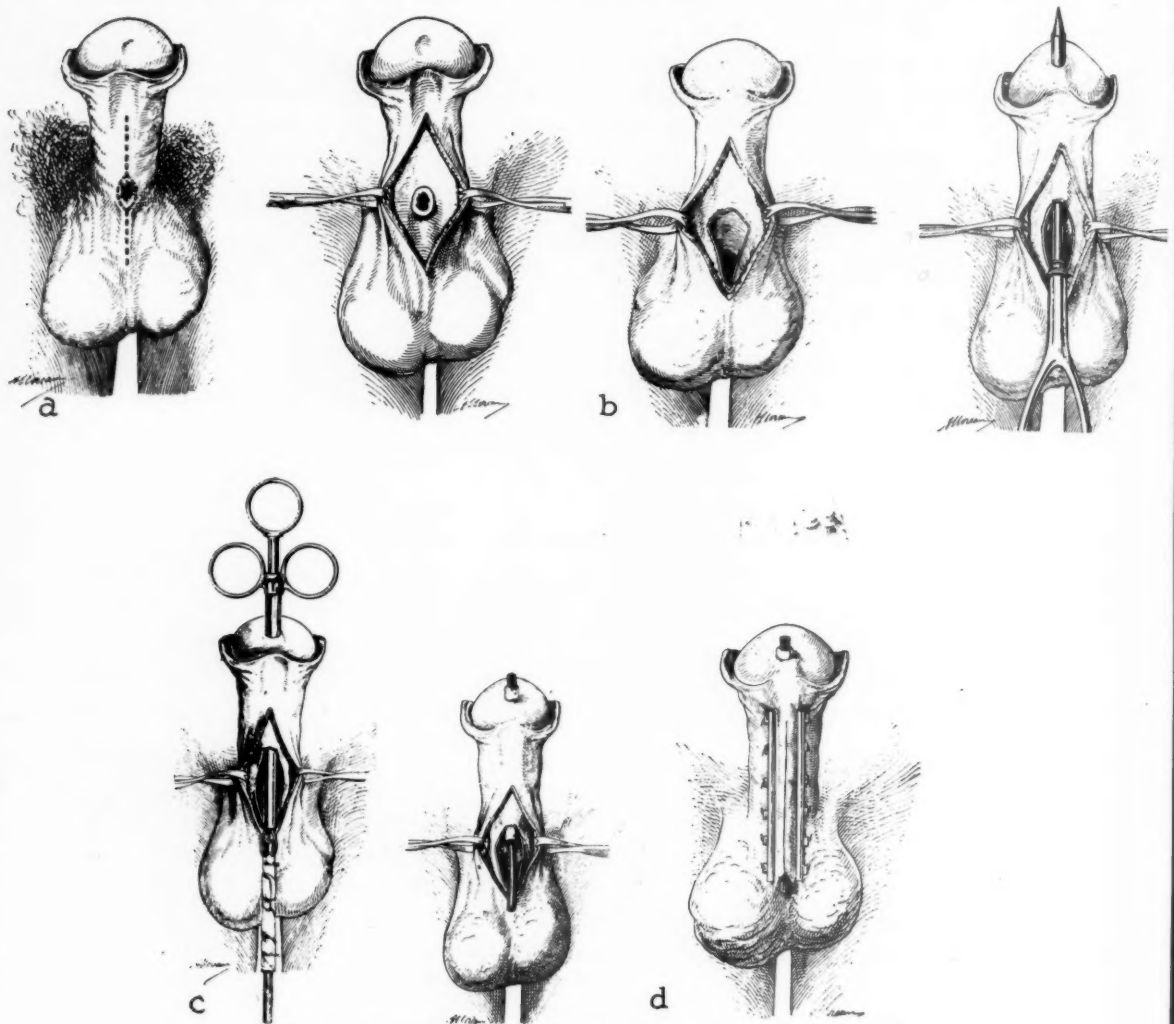

Fig. 1.—Reproduction of illustrations from Nové-Josserand.

5. Ombrédanne, 1911.[38] The chordee is corrected at a separate operation. The urethra is made by an elliptical incision on the ventral surface with the hypospadias meatus in about its center. This flap is turned forward with a purse string around its periphery in the form of a pouch enclosing the hypospadias meatus. The raw surface left on the ventral surface of the penis is covered by buttonholing the perputial hood, drawing the glans through the

hole, and suturing the hood on the ventral surface of the penis. The urethra ends at the frenulum. At a second stage it is prolonged to the tip of the glans.

B. *Construction of Urethra With Free Graft.*—

1. Nové-Josserand, 1897-1919[30-35] (Fig. 1). The chordee was corrected first. At a second operation a 2 mm. long incision was made in front of the abnormal opening of the urethra. A dull instrument was introduced through this opening and with it a subcutaneous tunnel made to the base of the glans. The anterior end of the tunnel thus made was perforated with a trocar. An Ollier-Thiersch graft was cut from the thigh. This graft was rolled on a No. 16 probe with its cutaneous surface inside. The clothed probe was introduced into the subcutaneous canal and kept in place by a convenient dressing. At the end of eight days the probe was withdrawn. Daily catheterizations were started to prevent contracture. This was kept up for about two months. The first patient operated upon was 18 years old. In 1914 Nové-Josserand reported the results obtained by this method in eighteen cases.

TABLE I. END-RESULTS REPORTED BY NOVÉ-JOSSERAND IN 1914

CASE NO.	TYPE OF HYPOSPADIAS	AGE (YR.)	RESULT
1	Penile-scrotal	21	Fistula followed 1 year
2	Penis	5½	Good, fistula small, 7 years
3	Perineal pseudohermaphrodite	12	Good, fistula small, 7 years
4	Penile-scrotal	5½	Very good, followed 12 years
5	Perineal	6	6 years, canal good, urine through fistula
6	Penis	3½	Stricture
7	Scrotal	14	Good, 7 year follow up
8	Penis	6	Good, 7½ years
9	Penile-scrotal	5	Good, 6 years
10	Penile-scrotal	7	Good, 6 years
11	Scrotal	20	Good, 6 years
12	Penile-scrotal	13	Stricture
13	Penile	9	Good, 5½ years
14	Penis	Adult	Fistula, 4 years
15	Penis (juxtascrotal)	13½	Good, 3 years
16	Penis	16	Stricture
17	Penile-scrotal	34	Stricture
18	Perineal	7½	Good, 18 months

2. Miscellaneous methods. Some tissues used for urethral reconstruction: saphenous or some vein, Legueu (1921); urethra, Schmieden (1909); appendix, Weitz (1915), McGuire (1927), and Axhausen (1918); vaginal mucosa, Legueu (1918).

RECENT PAPERS

Recent papers are concerned mainly with modifications of the procedures of Thiersch-Duplay, Bucknall, Ombrédanne, and Nové-Josserand.

Cecil[6] used Bucknall and Thiersch-Duplay procedures to repair hypospadias and fistula following Thiersch operation. Nahoum[29] used a one-stage Thiersch-Duplay procedure to correct chordee and mild hypospadias but the objection to this type of operation is that the suture lines are directly superimposed and lend to fistula formation. Brendler[4] leaves the glans widely open at the time the chordee is corrected in order to form an epithelized trough. Subsequently the urethra is constructed by the Thiersch-Duplay method.

Hand[19] combined the better features of the Thiersch-Duplay and Ombrédanne procedures. He is of the opinion that age is not a determining factor for undertaking this operation. Goodhope[17, 18] used a tube graft made from scrotal skin and suggested wire be used as suture material.

Smith and Blackfield[41] recommended the correction of the chordee at 18 months of age and then at a suitable time a reconstruction of the urethra by Thiersch-Duplay flaps covered by scrotal flaps (Blair operation[2, 3]). The old and new urethra are joined at a second operation. In twenty patients they carried fourteen cases to completion, seven of which were uncomplicated while in the remaining seven, one urinary fistula developed in each at the proximal end of the new urethra. Five of these fistulas were closed at a third operation and two at a fourth. Thirty-seven operations were necessary to complete fourteen cases.

Kiefer[22] utilized the Rochet principle of bringing a tube graft from the ventral penile surface out through the glans.

The Ombrédanne procedure has been used by Goldstein,[16] Muschat,[28] Barcat,[1] Loughran,[23] and others. Goldstein did not use a catheter in three patients, ages 30 months, 4 years, and 28 years, with penoscrotal hypospadias. Loughran presented the most critical review of a large series of cases over a long period of time. He studied fifty-nine cases of which forty-three could be traced. Twenty-nine cases were completed with twenty-four good results; but it is interesting that there were nine penoglandular, sixteen penile, and only four scrotal types in this series.

Memmelaar[27] utilized the bladder mucosa as a free graft to form the urethra in a one-stage repair of hypospadias. He objected to the use of a skin graft because of the danger of infection and stated, "When bladder mucosa is used a real source of infection is omitted, provided one is not dealing with some stage of cystitis." This seems like an unfounded statement to us. There are some objectionable features to this procedure, namely, (1) the skin along the penile shaft is laid wide open, and (2) the suture lines are directly over each other. In both instances, we believe that fistula formation is quite likely to occur.

A most instructive paper in regard to differentiating male and female in an extreme deformity is that of Howard.[21] He found that, "In penile hypospadias, the utricle is normal. In penoscrotal and perineal hypospadias, the utricle is markedly enlarged and may communicate with a well developed uterus."

DISCUSSION OF HISTORICAL PRINCIPLES

Chordee Correction.—In reviewing these past procedures it seemed to us that the following criticisms were valid. The common operation for chordee is the so-called Heineke-Mikulicz in which a transverse incision is made just anterior to the hypospadias meatus. The fibrous cord is removed and the transverse incision closed longitudinally. This corrects the deformity to a certain degree. In severe deformities, it is our experience that an adequate exposure of the entire shaft cannot be obtained. Some of the restraining fibrous tissue remains and the ventral skin cannot be satisfactorily lengthened. There is also moderate recontracture of the longitudinal incision. We have recorrected a number of cases which had moderate bowing following this procedure.

The Edmunds[14, 15] operation in which the preputial hood is shifted to the ventral surface of the penis is more satisfactory. It gives adequate exposure for a complete dissection of the chordee. There are two minor objections to it. The first is that it takes two stages; at the first operation a preliminary tubing of the hood is done to insure blood supply. We have done this operation in one stage but it is a little risky as the blood supply of the two flaps into which the hood is divided may not be entirely adequate. An operation which can be safely done in one stage is preferable. The midline scar down the ventral surface of the penis is somewhat objectionable. It tends to contract and the urethral reconstruction must be done under or, in the flap operations, around it.

Urethral Reconstruction.—The Dieffenbach and Thiersch-Duplay operations are prone to multiple fistulas forming along the suture line. If the hypo-

spadias is of severe degree the scrotal portion of the urethra will contain hair. The meatus is at the frenulum. The urinary stream is often abnormal due to the patulous meatus and it's abnormal location.

The Rochet principle is not good for the same reasons and, in addition, we felt certain that there would be circulatory difficulty at the distal end of a flap as long as needed with a necessarily narrow base.

The Bucknall operation's greatest objection is hair within the urethra. Otherwise it is probably foolproof. However, as in the other procedures, the meatus is abnormally located.

The Ombrédanne operation is based on sound ideas. The main objection is that it is not suited to the more severe type of hypospadias. If after chordee correction the hypospadias is in the scrotum, the urethra cannot be completely constructed by this method without reproducing some of the original flexion deformity. We feel that it is a good procedure for mild cases of hypospadias where there is little or no curvature and the meatus is near the frenulum. Even then the urethra is somewhat pouchlike and if a normal meatus at the tip of the glans is to be obtained, a second operation is necessary.

Of all the procedures the principle of constructing the urethra with a free inlay skin graft as first advocated by Nové-Josserand appealed to us most. It appeared to have the following advantages. The urethra would probably not contain hair; any length of urethral defect could be corrected; the urethra would end at it's normal location in the glans; the likelihood of multiple fistulas forming seemed small since the urethra was formed in a subcutaneous tunnel; the appearance of the penis would be near normal; and it might be possible to do the operation in quite young boys.

It is probable that reconstruction of the urethra by a free skin graft has never been widely used; first, because urologists who mainly attend these conditions were not familiar with the principles of skin grafting, and second, because as originally described the possibility of contracture of the constructed urethra was ever present. It is of interest that Nové-Josserand described free graft repair of hypospadias in 1897. The graft he used was an Ollier-Thiersch graft described and developed from 1872 to 1886 by Ollier and Thiersch.[36, 37, 43] It is well known that the thin Thiersch graft has a high percentage of contracture. Despite this, Nové-Josserand was able to obtain good results in nine out of eighteen cases which he reported in 1914.

The Nové-Josserand operation was revived in 1937 by McIndoe.[24, 25, 26] He corrected the chordee when the patient was at the age of 2 years. This was done by the Edmunds procedure, which necessitates two operations. At the first operation a tubed pedicle is prepared from the preputial hood. One month later the fibrous remnants of the corpora spongiosum are dissected out, the urethra is dropped back to its normal location, and the ventral surface of the penis covered with the previously prepared preputial hood.

He then waited to construct the urethra until the patient reached the age of 7 or 8. This was done in the manner first described by Nové-Josserand using a thin "razor" graft. The subcutaneous tunnel was made with a trocar,

and a catheter with a skin graft wrapped around it was introduced. A catheter was introduced into the bladder through the hypospadias meatus to prevent urine coming in contact with the graft. McIndoe said, "At the end of ten days the casing is removed. The gum elastic catheter is withdrawn and the skin lined urethra syringed through with saline or half-strength ensol. A permanent dilator of suitable size is then introduced into the new urethra and at no time is this left out for more than the five or ten minutes required to cleanse the canal. It is necessary to make this point absolutely clear to the patient and the parents for twenty-four hours without the catheter will cause hopeless stenosis of the cavity in the early stages." After six months the dilator is left out and the epithelized canal is joined to the urethra after urinary diversion by external urethrostomy. Assuming that all steps go well this plan takes four operations and in our experience the joining of the urethra to the canal is not always successful.

Havens[20] has advocated the McIndoe operation but insists that the urethra should not be constructed until the age of 16 years. We would agree that continuously wearing a dilator for six months would be impossible in a 2- or 3-year-old boy, perhaps difficult to accomplish in a child of even 7 or 8. The operation seems more applicable to adults or the late teens.

As we know, skin grafts have greatly improved since Nové-Josserand's day so that more uniform grafts with less tendency to contract are now available. In addition, the Foley indwelling catheter as well as chemotherapy and antibiotic methods of controlling infection have been devised. All of these factors caused us to believe that it was feasible to attempt to construct the urethra in one step even in small children.

OPERATIVE PROCEDURE

Correction of Chordee.—As in all reconstructive procedures, a method gradually evolves and our experience is no exception. The steps reported are those we are now using. In brief, we attempt to correct the chordee at one operation. This is done quite early, if the patient is seen in infancy, at about 1 year of age. In this respect most surgeons concerned with correction of chordee seem to agree. The advantages have been enumerated many times but for the sake of clarity they are: (1) The chordee should be completely corrected before the urethra is reconstructed. (2) Early correction of the deformity permits earlier urethral reconstruction. (3) Growth proceeds normally. (4) Deformities in general are most easily corrected before they become fixed by growth.

The objective of the first operation is to obtain a straight penis with lax skin on the ventral surface and, if possible, a plan which will prevent recontracture to any extent. In addition, we have found that it helps prevent fistula formation when the urethra is constructed if the urethral orifice is off the midline (Fig. 2, *b*).

The first step is to dissect free the urethral opening. This dissection is carried proximally depending on the extent of the contracture. In any event one must be certain to excise all of the fibrous tissue which holds the penis

in the curved position. The urethra is freed by a circular incision and the dissection freeing it is done with a sound in place. When the proximal extent of the fibrous band is located, the urethra is retracted out of the way with stay sutures. An incision is made in the midline from the circular opening, left by

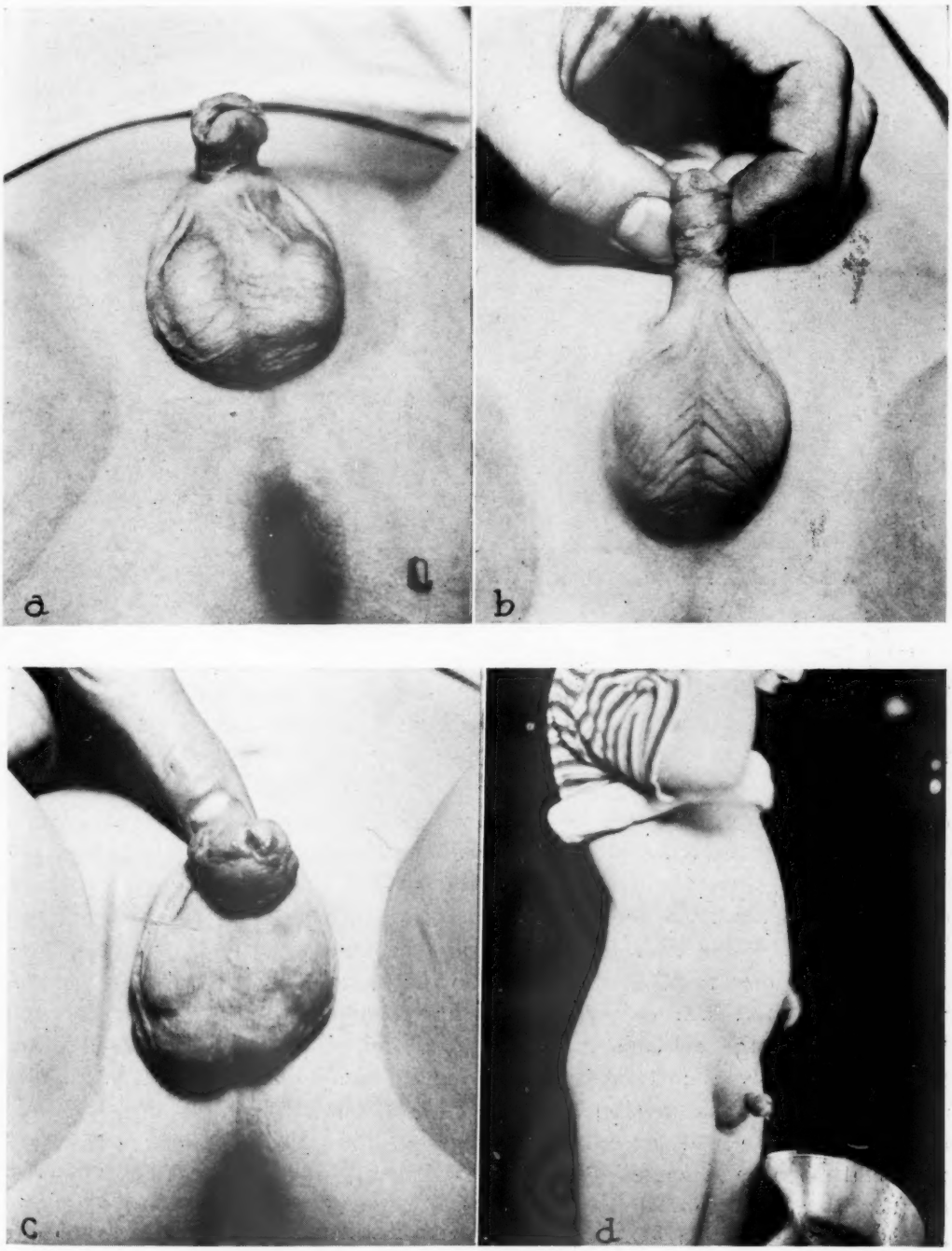

Fig. 2. (Case 8).—*a*, Mild penile type of hypospadias with usual chordee. *b*, Chordee corrected; skin on ventral surface lax and urethral orifice well off midline. *c*, Appearance of reconstructed meatus. *d*, Five-year-old child voiding through reconstructed urethra.

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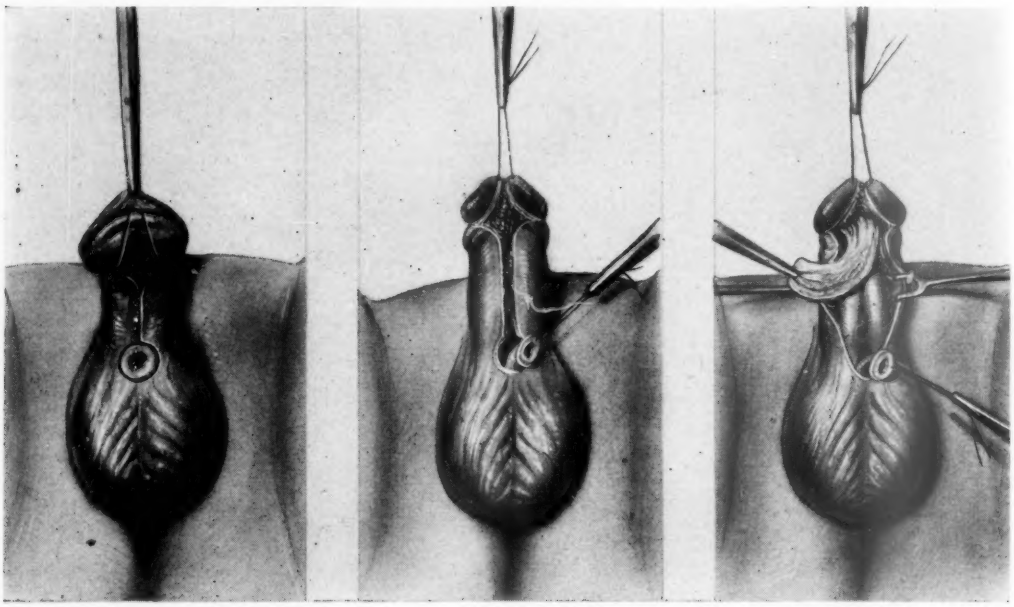
freeing the urethra, to the frenulum. At this point the incision branches to either side following the mucocutaneous line. It then elliptically encloses the groove in the flattened glans. We did not originally do this but found that by so doing the flattened glans could be made more presentable when the two sides were brought together and sutured (Fig. 3, *a*).



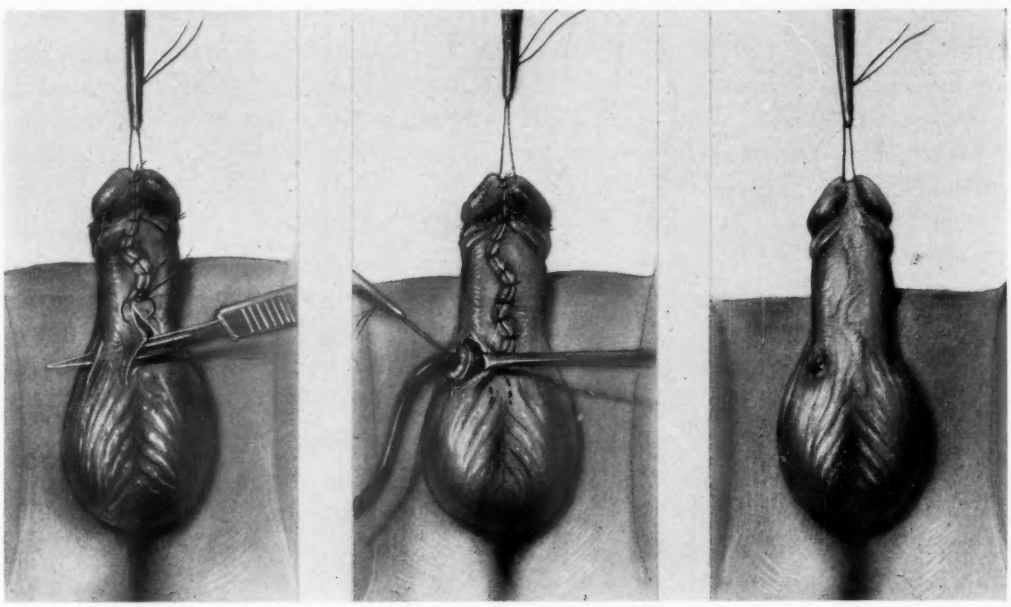
a. *b.* *c.*

Fig. 3.—*a*, The incisions for correction of chordee and flattened glans. *b*, The urethra is dissected free, the skin undermined laterally for complete exposure of the contracture, and the sulcus in the glans excised. *c*, Excision of fibrous tissue producing chordee; the corpora are completely freed. Buck's fascia is crosscut or partially excised.

The skin on either side of the incision is freed, thus exposing the contracted tissues. The fibrous band is dissected out beginning either proximally or distally as is expedient. The dissection of the band proceeds along the corpora cavernosa and must be quite close to it. In some instances, Buck's fascia seems contracted and in order to secure complete straightening of the shaft must be crosscut, or even partially excised. At this stage the corpora cavernosa are plainly seen. The urethral orifice has dropped backward and it should be possible to hyperextend the penis without any ventral tightness (Fig. 3, *c*). Once the deformity has been corrected, one must attempt to prevent postoperative scar contracture causing a partial return of the deformity. If the skin of the penis is closed longitudinally as in the Heineke-Mikulicz principle, this is almost certain to happen. To avoid this, the closure is staggered in multiple fashion by imbrication of triangular flaps (Fig. 4). We originally set the urethral opening off the midline by enclosing it in the most proximal of these zigzags, but found that it could be more efficiently done by making a small stab wound through the skin well laterally and sewing the urethral end into this (Fig. 4, *a* and *b*). There is a mild tendency for this circular wound to contract, but a few passages of small sounds during the first one or two months is sufficient to overcome this. The importance of a

lateral wound to work through when later fashioning the urethra is sufficiently great to warrant this slight inconvenience.

Sufficient skin for the added length of the ventral surface of the penis is usually obtained by the combination of wide lateral undermining, cross-cutting and triangular inserts, and some shift from the hood which occurs from the correction of the deformed glans and the mucocutaneous incisions spreading laterally on either side of the frenulum (Fig. 4, *c*). We have occasionally shifted the preputial hood by making a dorsal slit in the hood, dissecting off and discarding the mucosal surface, and rotating the halves of the hood skin to the ventral surface. This should not be routinely done. In a severely deformed penis with perineal hypospadias and vulviform scrotum we have on one occasion corrected the bifid scrotum at the same time the chordee was corrected by transplanting the two scrotal halves downward.



a. *b.* *c.*

Fig. 4.—*a*, The halves of the glans are brought together and the skin closed in multiple Z form to prevent later contracture. There is some shift of the hood ventrally to more nearly resemble the normal prepuce. A small stab wound is made laterally. *b*, The free urethra is brought out the lateral stab wound and surtured to its edges. *c*, The healed zig-zag scar with urethral orifice laterally.

After the skin has been closed the glans penis is sutured to the abdominal skin in extended position, a Foley catheter is introduced through the urethral opening to the bladder to prevent urine flowing over the suture line, and a compression dressing is applied over the penis to prevent edema and possible hematoma formation. This dressing is left on for four or five days. The catheter is removed when the wound is well healed, usually in about seven days. The suture is released from the abdominal wall a little later or when it breaks. In all children it is imperative that the child be in bed with the extremities restrained. We have not found that erections are particularly troublesome in either children or adults when a compression dressing is used and have not used any specific medication in an attempt to prevent them.

Construction of Urethra.—A varying period of time must be allowed to elapse for the tissues to soften thoroughly before the urethra is constructed. The minimum time is usually about six months. Before one begins the urethral construction, there must be minimal curvature of the penis, otherwise the organ will not be satisfactory sexually even though a urethra is present. The patient is followed at about monthly intervals, noting any tendency of the penis to curve on erection and watching the state of the tissues to determine when urethral construction can be undertaken. If the child is around 1 year old when the chordee is corrected, we usually wait until he is about 2 or 3 years of age before making the urethra. This gives plenty of time for complete return of the tissues to normal and since the objective is to obtain normal urination before school age, no time is lost. In adults the minimum time of six months may be a sufficient waiting period.

There has always been a difference of opinion as to whether or not to divert the urinary stream and the method to be used. We think it is only common sense to keep urine off the healing tissues, not so much because of infection but because of maceration. A perineal urethrostomy is simpler to do than a suprapubic cystotomy and with an indwelling Foley catheter is quite efficient.

The first step in urethral repair, therefore, is the urethrostomy performed high in the perineum. This site is chosen with the definite purpose of causing the urine to flow past the urethrostomy at more or less of a right angle rather than directly toward it, which occurs if the opening is lower where the urethra turns. We believe that this helps in prompt closure of the perineal urethrostomy after the catheter is removed (Fig. 5).

The urethral orifice previously placed off the midline is encircled by an incision and is dissected free for about one-half inch. This dissection is made well past the midline to allow the constructed urethra to return to the midline. A tunnel is made with scissors distally under the skin toward the glans. At the frenulum one must proceed carefully since the skin is thinner and more attached. The tunnel is carried through the glans emerging at the dimple where the normal meatus should be located (Fig. 7). A skin graft about 0.020 inch thick is cut by the dermatome from the anteromedial aspect of the upper arm (Fig. 6, *a*). This area is as nearly hairless as any obtainable. In 2-year-olds this 0.020 inches may be greater than the thickness of the skin. The graft should be almost but not quite full-thickness. After the first cut the dermatome should be reset if subcutaneous fat is seen. This graft is secured with dermatome cement to a catheter ranging in size from No. 14 to No. 18 French depending on the age of the individual and the size of the penis. At either end a No. 0000 chromic catgut tie encircles the graft and catheter to prevent rolling when the catheter and graft are introduced into the tunnel (Fig. 6, *b*). Introduction is through the opening in the glans, the tip of the catheter being pulled on downward into the urethra. The catheter is turned so that the seam of the graft is dorsal. The tunnel should be of such size as to hold the graft-covered catheter snugly. The tie around the introduced end of the graft

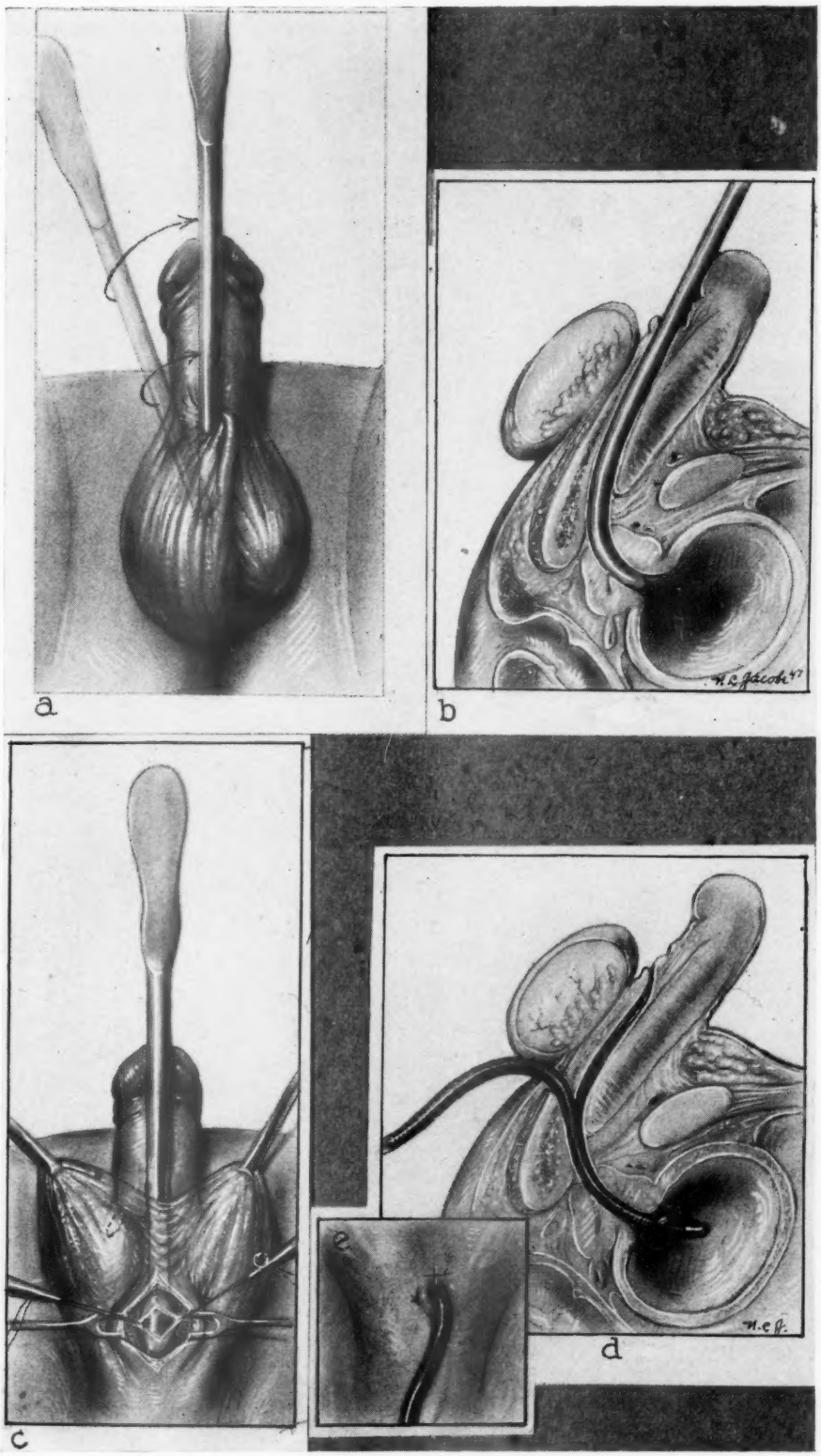
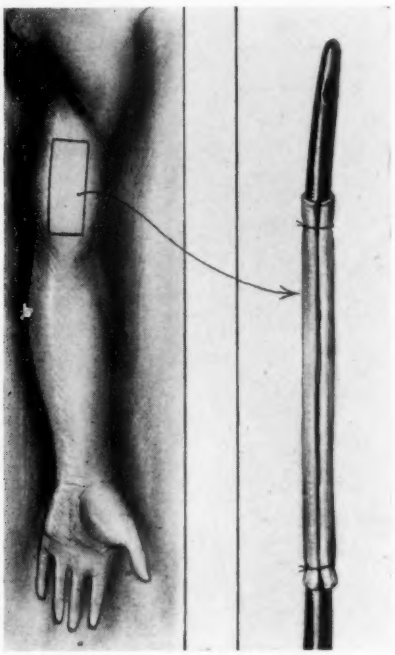
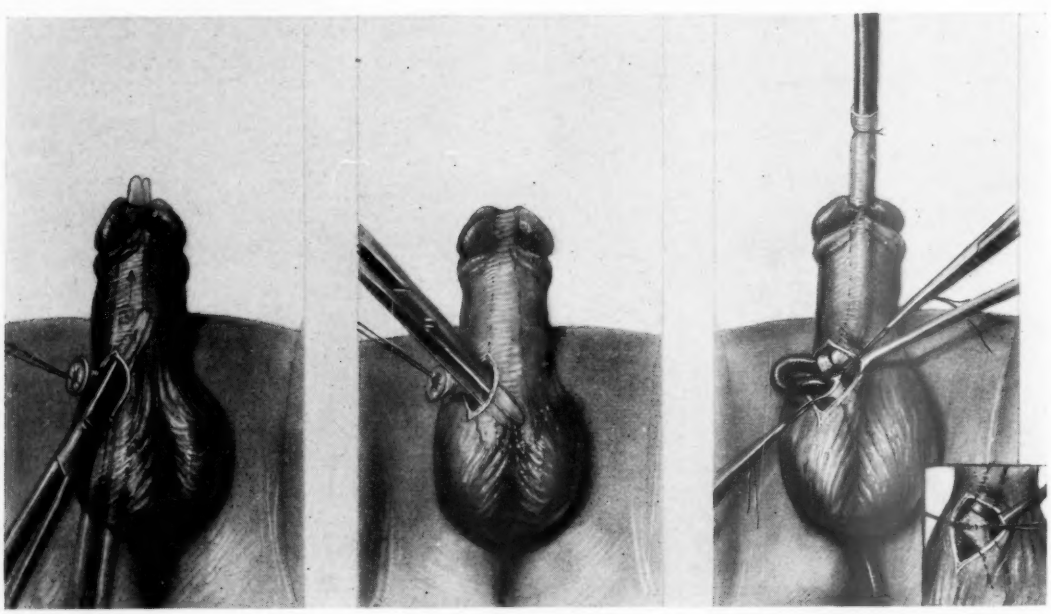


Fig. 5.—*a* and *b*, First step in urethral construction, sound in place. *c*, Urethra opened rather high in perineum. *d*, Foley catheter in place. *e*, Wound closed snugly around catheter.



a. *b.*

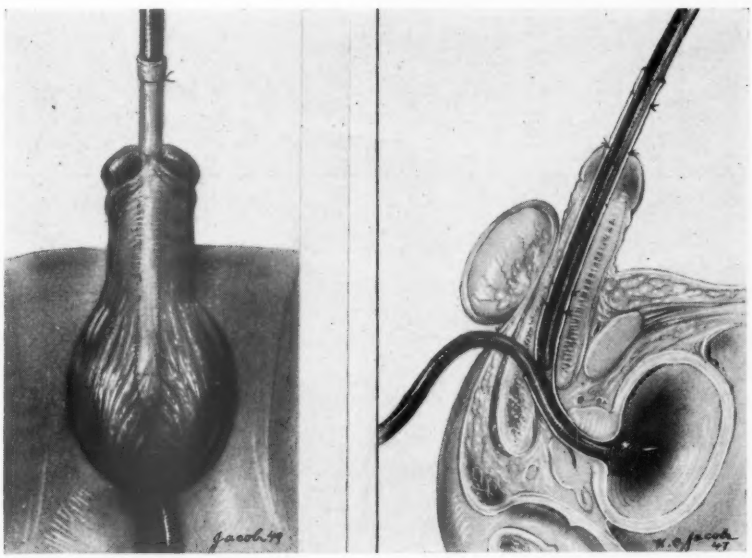
Fig. 6.—*a*, Free graft cut with dermatome from hairless anteromedial surface of upper arm. *b*, Graft fixed on catheter with dermatome cement. The two ligatures are to prevent rolling on introduction into tunnel. The tie, at the end which is sutured to the urethra, is removed after introduction. If the section of urethra to be constructed is short, the preputial skin may be used for the graft.



a. *b.* *c.*

Fig. 7.—*a*, The end of the urethra is freed by an encircling incision and a tunnel made under the skin and glans. *b*, The urethra is thoroughly freed proximally and the tunnel completed medially and proximally. *c*, Inlay graft in place and end of graft bearing catheter introduced into urethra. The graft is joined to the urethra with 0000 atraumatic chromic catgut sutures. The tie around the catheter is removed after suture is completed.

is then removed since it has served it's purpose. The graft and urethra are sutured with interrupted No. 0000 chromic catgut sutures on atraumatic needles (Fig. 7, *c*). Since the urethral opening was off the midline, the graft-covered catheter comes to rest under a bridge of skin when dissected free. The closure of the opening is accomplished by suturing the deep tissues and then closing the skin with on-end mattress sutures. This provides a folded surface for healing rather than edge-to-edge approximation. The object is to keep the suture line of urethra-graft anastomosis and skin away from one another since this is the place where fistula formation is most common. The penis is elongated as much as possible by sliding it over the graft and a stitch transfixes the glans, catheter, graft, and abdominal skin. Thus the penis is held in hyperextension (Fig. 8).



a. *b.*

Fig. 8.—*a*, Completed urethral reconstruction. The suture lines of graft-urethra anastomosis and of lateral wound do not coincide. *b*, Sagittal section showing relationships of catheter, ligatures, and suture lines.

The position on the abdomen facilitates the application of a compression dressing. Originally we immobilized the legs in an abducted position with plaster but we no longer do this as a simple compression dressing seems effective. This is applied with cotton, voluminous gauze, and elastic adhesive. In children the arms and legs are restrained. Originally we kept the graft-bearing catheter in the penis for fourteen days and the perineal catheter for three or four days longer. As we gained more experience this time has been gradually decreased. We noted that at six or seven days there was often mucopurulent discharge at the glans meatus and similar discharge at the suture line on the shaft. Therefore, we at present remove the catheter from the penis when it is no longer firmly adherent to the graft and the indwelling perineal catheter on the same or next day. The patient is allowed to void in order to wash out the discharge. A catheter may then be inserted through the penis into the bladder if the perineal urethrostomy does not close in two or three days.

TABLE II. ANALYSIS OF SIXTEEN CASES WITH IMMEDIATE AND LATE END-RESULTS

CASE	HOSPITAL UNIT NUMBER (S.M.H.)	TYPE HYPOSPADIAS	AGE CHORDEE CORRECTED		AGE URETHRA RECONSTRUCTED	IMMEDIATE RESULTS	FINAL RESULTS
			ELSEWHERE	OUR CLINIC			
1. J. S.	164068	Perineal		18 mo.	3 yr.	Small fistula	Fistula operatively closed at 4 yr.; excellent at 10 yr.
2. H. B.	194501	Scrotal	Completed		39 yr.	Intact urethra	Excellent at 6½ yr.
3. J. C.	196052	Scrotal	Partially corrected		Chordee corrected and urethra constructed in one stage, 38 yr.	Pressure necrosis from dressing; large fistula	Fistula operatively closed 8 mo. later; small sinus remained which closed; no follow-up
4. G. P.	229669	Scrotal	Completed at 9 yr.		10 yr. (preputial graft)	Small fistula	Fistula operatively closed at 12 yr.; intact urethra, good stream at 12½ yr.
5. J. B.	221596	Scrotal	Incomplete at 1 yr.	11 yr.	12 yr.	Intact urethra	Excellent 3 yr. after repair
6. A. S.	233230	Scrotal	Incomplete at 24 yr.	24 yr.	25 yr.	Intact urethra	Excellent 1½ yr. after repair
7. D. R.	238687	Scrotal	Complete at 10 yr.		11 yr.	Small fistula	Voids 95% through the glans; very tiny fistula 2 yr. after repair
8. B. F.	247264	Penile		4 yr.	4½ yr.	Intact urethra	Perfect 2 yr. later
9. W. C.	236358	Penile		8 yr.	9 yr.	Small fistula	Fistula operatively closed at 9½ yr., good; 1-2 drops in perineum on urination 1½ yr.
10. R. S.	168824	Perineal pseudo-hermaphrodite		7 yr.	7⅓ yr.	Small fistula at both urethral anastomosis and perineal urethrostomy	Two different attempts to close fistula, second successful but patients gets ballooning of skin over fistula on urination
11. R. G.	214778	Penile		5 yr.	6 yr.	Intact urethra	Excellent 6 mo. later
12. J. K.	262485	Scrotal	5 previous operations for chordee and urethral construction; chordee corrected		9 yr.	Large fistula	Fistula successfully closed 1 yr. later; excellent 6 mo. later
13. D. C.	223514	Perineal pseudo-hermaphrodite		1 yr.	3 yr.	Moderate fistula	Bifid scrotum corrected, fistula closed; excellent 1 yr.
14. R. D.	243198	Penile		1 yr.	2 yr.	Tiny fistula	Few drops from anastomotic site 6 mo. after repair
15. L. G.	231218	Penile		2 yr.	4 yr.	Tiny fistula	Few drops from anastomotic site 2 mo. after repair
16. D. B.	13304	Perineal	13 previous operations for chordee and reconstruction of urethra		19 yr.	Large fistula	Fistula operatively closed 1 yr. after urethral construction, result tiny fistula; 75% urine through meatus

IMMEDIATE AND LATE RESULTS OF CHORDEE CORRECTION (TABLE II)

We began this type of repair in 1940, nine years ago at the time of writing. In that period we have corrected twenty-five chordees. It has been necessary to reoperate in one case. In this instance there was partial slough of the tip of one triangular shifted from the hood. The scar healing caused some recontracture but was mainly corrected secondarily because we did not think it would stand the tunneling and pressure necessary for urethral reconstruction. We rarely find it necessary to secure skin from the prepuce at the present time. The hood is drawn ventrally to a certain extent by correcting the ventral furrow in the glans and is transformed into an almost normal looking prepuce. From this series of twenty-five cases it is evident that the plan as outlined for chordee correction is completely satisfactory. In no instance has there been an appreciable return of curvature of the penis on erection. This can be easily determined even in a 2- or 3-year-old by intentionally causing an erection during examination by handling of the organ.

TABLE III. SUMMARY OF RESULTS OF CHORDEE CORRECTION

NUMBER OF CASES	RESULTS
24	Successfully corrected in one operation
1	Successfully corrected in two operations (Second operation to correct scar contracture following partial slough of a triangular flap)
25	Total cases

RESULTS OF URETHRAL CONSTRUCTION

Immediate.—In the sixteen patients in whom the urethra has been constructed at one operation, five have had healing per primam with no leakage at any time and have voided through an adequate orifice in the glans penis as soon as the catheters were removed (Fig. 2). These we class as excellent immediate results. In the other eleven cases there has been some leak at the anastomosis of urethra and graft. This has varied from a sinus so small that it could not be seen without diligent search and allowing only a few drops to moisten the site on urination, to a large obvious fistula allowing most of the urine to pass through. In all but four of these eleven cases the fistula has been quite tiny.

Late.—The five immediate excellent results have remained so. Of the eleven others, in three the fistula was tiny and so shrunk with time that only two or three drops of moisture were evident on urination. In these cases further surgery was not considered advisable. These patients could urinate standing without wetting the clothing and with a completely adequate stream. Of the eight remaining cases, in five the sinus was completely closed by a second operation. In one case there were still a few drops even after the second operation for sinus closure but again, as he could stand to void satisfactorily, further surgery seemed questionable.

Thus out of sixteen cases, eight have had satisfactory results in one operation and six in two operations.

Of the two remaining cases there is still about 25 per cent of the urine coming through an anastomotic fistula after two operations. A small fistula awaits closure at a third operation. This patient had been operated upon thirteen times previously in our own clinic, when he was from 2 to 16 years of age, by the Thiersch-Duplay technique with little success; the tissues were consequently quite scarred.

The remaining case is the only one we would class as a poor result. The patient was pseudohermaphroditic, with a hernia and an undescended testicle on one side. The perineal urethrostomy had to be made far down in the perineum. It did not close and an anastomotic fistula also remained. Two different attempts were necessary before the two fistulas were closed. However, an internal fistula still remains since the skin balloons on urination and he has periodic bouts of periurethritis.

TABLE IV. SUMMARY OF RESULTS OF URETHRAL RECONSTRUCTION

NUMBER OF CASES	RESULTS
5	Perfect urinary function in one operation
5	Perfect urinary function in two operations (second operation to close anastomotic fistula)
3	Good urinary function in one operation (one to two drops of moisture at anastomosis on urination; further surgery unwarranted)
1	Good (similar criteria) in two operations (one to two drops of moisture following anastomotic fistula closure)
1	Fair (75% urine through meatus, 25% through fistula after two operations)
1	Poor; three operations (second and third to close fistulae); has no leak but urethra balloons over site of fistula, has periodic periurethritis
16	Total cases

DISCUSSION

From these data it is evident that one can expect from these procedures a straight penis on erection in one operation. If the urethra is constructed in this way one can expect about one out of three patients to urinate normally after the initial operation and about 50 per cent to urinate satisfactorily.

It is worth noting that in no instance has there been a failure of the inlay graft taking. Furthermore, fistula formation when it does occur is limited to the site of the urethral-graft anastomosis. If a fistula occurs, it is not wise to attempt immediate closure, although scarification of a tiny tract may occasionally be followed by complete healing. The fistula will spontaneously shrink and if the tissues are thick and the urethra somewhat removed, complete healing may occur as long as three to four weeks after operation.

If an anastomotic fistula persists, some months must elapse for the tissues to soften completely before an attempt is made at closure. If this is done, over 50 per cent of the fistulas can be completely healed at the second operation. In the over-all picture one can expect ten out of sixteen patients to urinate in a completely normal fashion and of the remaining six, four will have satisfactory urination.

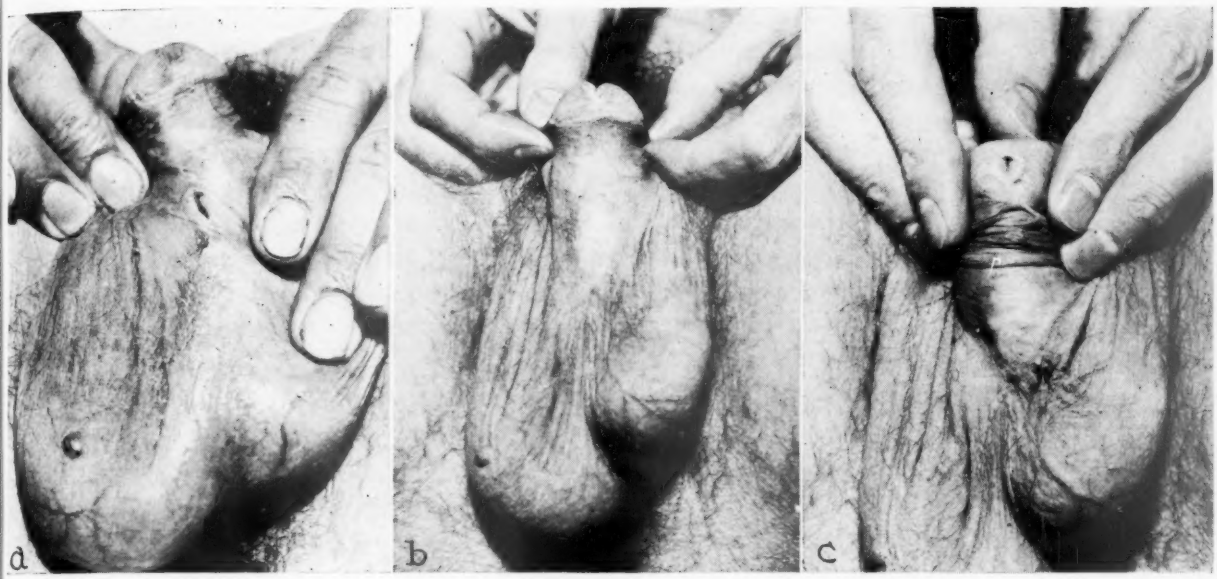


Fig. 9 (Case 2).—*a*, Condition in which patient first presented himself. Chordee had been satisfactorily corrected elsewhere. *b*, Ventral view following urethral construction. *c*, Reconstructed meatus in glans.

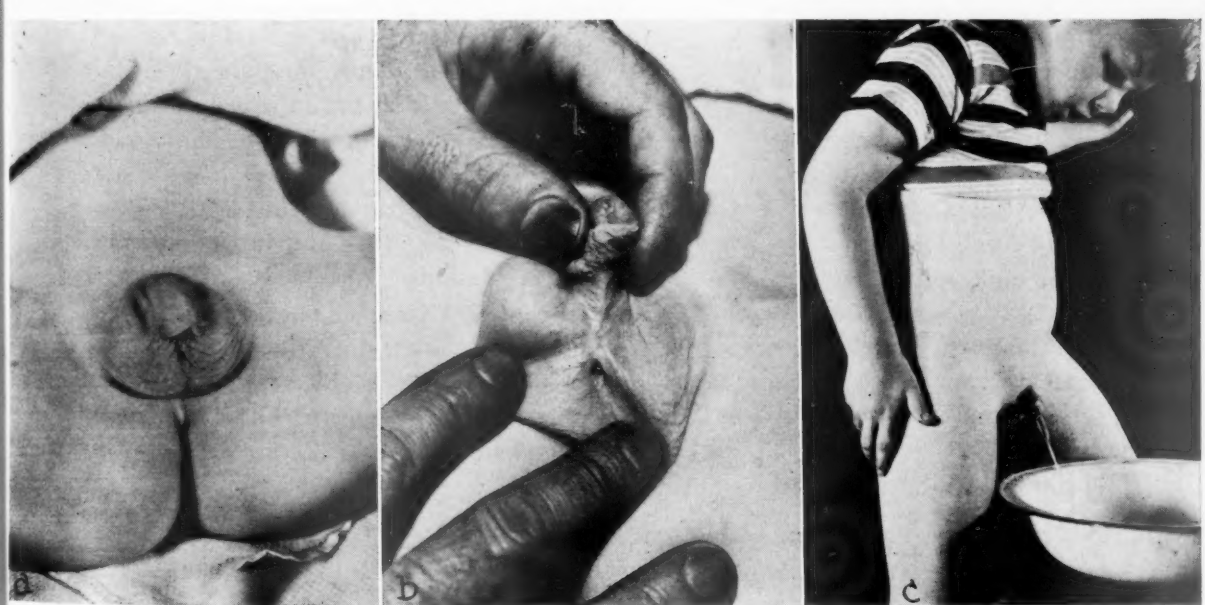


Fig. 10 (Case 1).—*a*, An extreme pseudohermaphroditic deformity, the penis is completely adherent on its ventral surface. *b*, In this type of deformity the urethral orifice remains far posteriorly in the perineum when the penis is straightened. *c*, Final result; good urinary stream five years after urethral reconstruction.

We believe that in the past the main reason for not using a free graft for urethral construction has been the fear of contracture and stricture. A follow-up of our cases does not bear this out. At first we also had this lurking fear and dilated the constructed penile urethra frequently. We noted that this was often accompanied by bleeding, and of course, considerable discomfort. Because it seemed that the continual trauma would predispose to more scar tissue formation we abandoned frequent dilation and to our surprise found that the caliber of the stream in most instances improved. Evidently the urinary stream is sufficient in those instances where it passes through the urethra. If most of the urine comes through an anastomotic fistula, more frequent observation and passing of sounds to determine whether dilation is necessary is advisable. The caliber of the stream is the best indication and, on each follow-up visit, the patient should be observed voiding if possible.

We have now observed two patients for nine years since construction of the urethra. Fortunately, for our purpose, one of these was a child 3 years old at the time of repair and the other an adult 39 years old. The child has maintained a completely satisfactory urinary stream and growth of the penis (Fig. 10). No tendency to stricture or for the chordee to return has been observed. This would seem to indicate that the graft has maintained a normal growth rate. The adult has developed no stricture and, according to both him and his wife, sexual function is normal (Fig. 9).

Both of these patients have been endoscoped. The graft in each instance bears a close resemblance to urethral mucosa. There was no hair present. At the site of the anastomosis a circular ridge was observed through which the instruments passed easily. It may be argued that the organ will become bowed as it becomes larger in adult life. Our opinion is that this will not occur. We know that skin grafts grow with the individual in other locations and presumably will here as well. We have watched our first patient grow from 3 to 12 years of age and there is no chordee on erection.

It has also been suggested that any tissue other than penile is not satisfactory for urethral construction because it does not have sufficient elasticity to stretch with erection. In Case 2 sexual function has been satisfactory for eight years. One patient (Case 6) married shortly after operation and had no difficulty. We believe constructing the urethra with the organ hyperextended and elongated and some stretching of both the old and new urethra by erections will contribute to satisfactory urethral length with the organ erect. This question will be finally answered when the 2- and 3-year-old children are 18 and 20 years of age.

SUMMARY

1. The chordee deformity of hypospadias can be completely corrected in one operation when the patient is 1 year of age. This is accomplished by complete exposure of the corpora cavernosa, excision of the fibrous remnants of the corpus spongiosum, the furrow in the glans, and often of part of Buck's fascia. The urethral orifice is transplanted laterally and backward, the halves of the glans and prepuce brought together, and the skin closed in zigzag fashion. In twenty-five cases there has been one reoperation.

2. The urethra can be reconstructed in a 2- or 3-year-old patient in one operation. This is done with a free inlay skin graft.

3. The method makes multiple operations unlikely. In sixteen patients, ten have had a perfect result, four satisfactory, one poor, and one unfinished. Twenty-five operations have been done in these sixteen patients in constructing the urethra.

4. The advantages of this operation over the usual flap operations, or the original Nové-Josserand or McIndoe's modification of it, are many. The urethra has a normal exit in the glans penis, the urinary stream is therefore more normal, and the appearance of the organ better than in penile flap operations. The urethra does not contain hair as in most of the flap operations. Following flap operations it is not uncommon to have complete failure or multiple fistulas form. The poorest result in this regard when the urethra is constructed with a free graft is a fistula at the anastomosis of the graft and the urethra. The method avoids the two stages necessary in the Nové-Josserand operation and the risk of stricture or the prolonged wearing of a dilator as in the McIndoe operation.

5. We have had no case in which stricture has occurred, and prolonged and frequent dilation of the urethra has not been necessary.

6. Finally, and most important of all, operation is applicable to preschool age children and can be used for any degree of hypospadias.

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A METHOD FOR CONTROLLING URINARY INCONTINENCE

Experimental Observations

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MANY children with lumbosacral myelomeningoceles have neurological disturbances in the lower extremities, with accompanying urinary and fecal incontinence. The urinary incontinence is in some respects the most serious problem that confronts these patients. It prevents them from engaging in normal activities and the resulting urinary tract infection is a frequent cause of death. Some of these children, who have relatively minor cord lesions, with adequate function of the lower extremities, are prevented from living a normal and useful life only because of urinary dribbling.

Attempts to train these children to acquire urinary control through the development of a reflex urinary bladder have not been encouraging. This failure is particularly discouraging in comparison with the excellent results obtained in treatment of urinary incontinence associated with traumatic lesions of the lower spinal cord.[1, 2] This difference may be more apparent than real, since long-range programs used for treating paraplegic patients at the Army and Veteran's Administration Hospitals have not been equaled in civilian practice. However, the anatomic lesion of the cord in myelomeningocele differs from that in traumatic transection of the cord, and therefore the possibility that prolonged training can achieve a reflex bladder in children with congenital anomalies of the lower spine is questionable.

Traumatic lesions of the spinal cord usually destroy but a short segment, and normal cord below the transection is capable of playing its role in the function of the reflex bladder. Myelomeningoceles, on the other hand, are usually associated with disruption of cord structures over a long segment, and there may be no anatomic possibility of a reflex type of bladder. At the present time attempts to produce reflex bladders in children with cord damage are being carried on but have so far proved unsuccessful.[3]

At the present time there is no satisfactory technique for the relief of urinary incontinence in these children. Transplantation of the ureters into the colon is not feasible, for practically all of the patients have an associated incontinence of the anal sphincter. In this clinic attempts have been made to construct a bladder by utilizing the sigmoid colon in several patients. This procedure consisted of implanting the ureters into an isolated loop of sigmoid colon which in turn was drained through the abdominal wall. In some of these patients the isolated loop serves as a reservoir and by intermittent catheterization the patients remain dry. Other patients in this group constantly leak urine

Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 24-26, 1949.

from the fistula despite intermittent drainage. Other methods of dealing with this problem have proved ineffective.

One solution would be the establishment of an external urinary fistula which could be controlled. Such a fistula would allow emptying of the bladder at intervals, and permit closure of the urethra, thus preventing the dribbling of urine.

Studies were first undertaken to determine the ability of the abdominal wall and urinary bladder to tolerate a plastic tube. In nineteen dogs, sections of polyethylene tubing with solid flanged ends were inserted through the abdominal wall into the bladder.

In seven animals the tubes were too short and had inadequate flanges; consequently one end pulled out of the bladder and the other end retracted below the skin. In twelve dogs, longer tubes carrying wider flanges were used. These tubes maintained their position. Observations covered periods as long as seven months. Leakage of urine did not occur and the tubes were tolerated with little reaction in the abdominal wall and bladder.

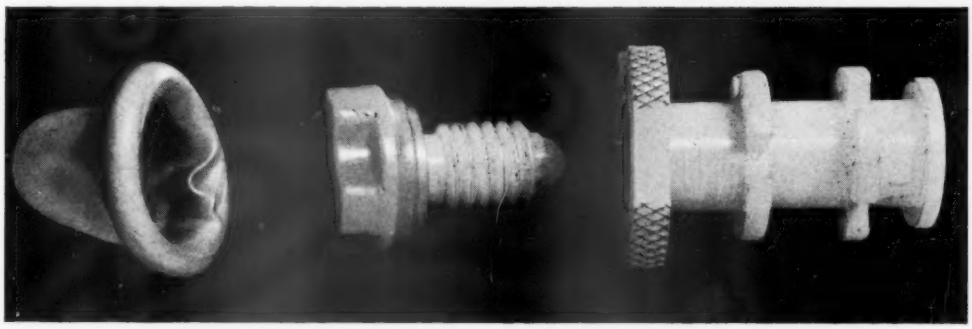
This experience encouraged us to insert a plastic valve mechanism into the bladder in a second group of dogs. Nylon, now obtainable in rod form, was selected as the most favorable material to use in the construction of a valve. Its tolerance by body tissue is established,[4] and its great tensile strength,[5] toughness, and durability, combined with its light weight, made it the ideal material for our purpose. Furthermore, this plastic can be autoclaved.[6] Several designs were tried, and finally it was demonstrated that a simple two-piece, manually operated valve was most dependable. This valve consisted of a housing which was a tube with flanges at both ends. The outer flange was of greater diameter than the inner and was knurled to facilitate operation of the valve. The inside of the housing was threaded and a narrowed portion or valve seat was incorporated. The second part of the valve mechanism was the valve stem. This consisted of a threaded rod with a smooth, rounded inner end and a knurled knob at its outer end. This rod was provided with holes which were so placed that when the valve stem was securely screwed into the valve housing a watertight seal was produced. One-half turn in a counterclockwise direction disengaged the valve stem from the valve seat and permitted a free flow of fluid through the mechanism. The hole in the outer end of the valve stem was threaded to permit attachment of a drainage tube (Fig. 1).*

Several problems were encountered in implanting the valve unit. In the first place, to prevent rotation of the valve housing during the operation of opening and closing the valve, projections were made on the housing around which the tissue could become firmly attached. The second and most troublesome problem was to prevent retraction of the prosthesis below the skin. Swelling of the abdominal wall usually occurred during the first few postoperative days after insertion of the valve mechanism, and it was during this

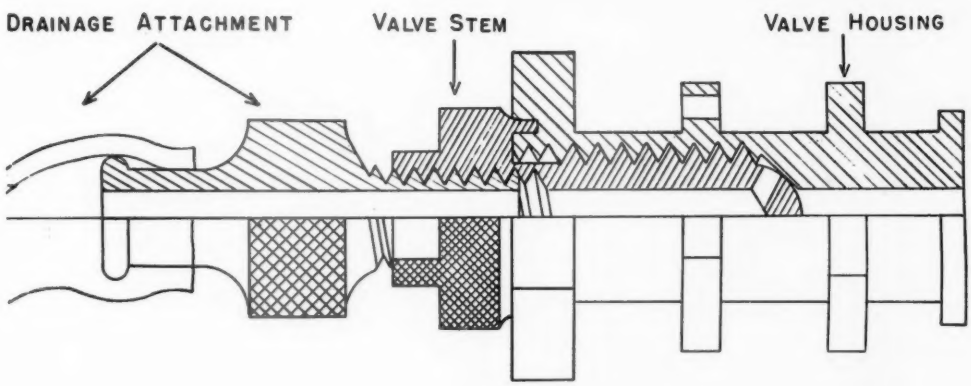
*This valve mechanism was developed with the help of Mr. Carl Hewson and was manufactured by the Brunswick Manufacturing Co., Boston, Mass.

period that it was most likely to retract beneath the skin. This difficulty was overcome by the use of a large flange on the exposed end of the valve housing.

Our routine was to insert the closed valve into the bladder and to secure it in place with two purse-string sutures. A small amount of the abdominal wall was excised in order to permit closure of the structures around the valve housing without tension or pressure on the tissue. This technique minimized edema, tissue necrosis, and infection. Provided due care in closure of the wound was taken, prompt healing occurred. When the prosthesis was firmly healed in place, the urethra was ligated and divided. This was usually performed about the tenth postoperative day. After the second operation the valve was left open for two to four days. This prevented the accumulation of urine in the bladder under pressure, which might result in the creation of a urinary fistula through the closed urethra. The valve was then closed and the bladder drained twice daily (Fig. 2).



A.

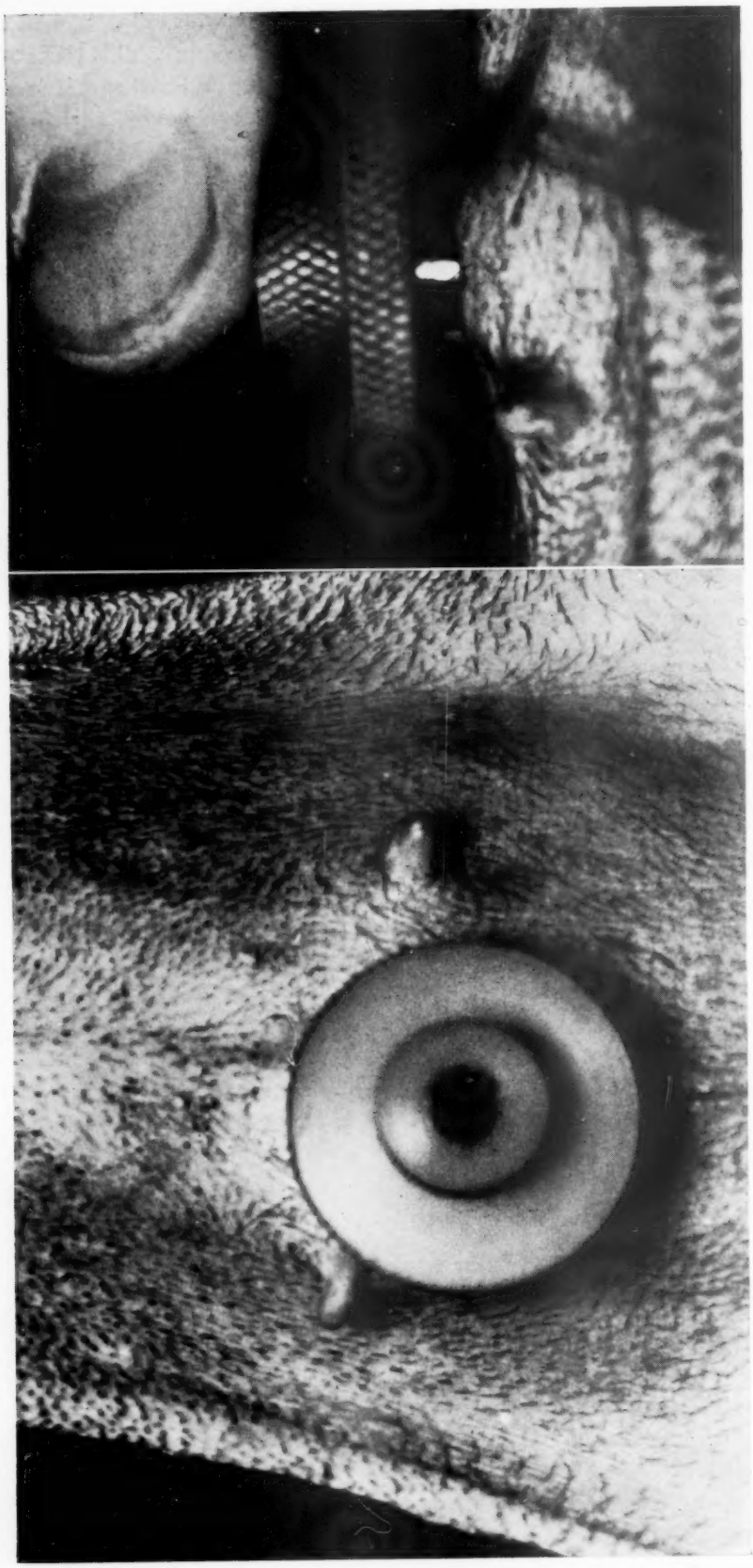


B.

Fig. 1.—*A*, "Exploded" view of nylon bladder valve. *B*, Construction details of bladder valve with drainage tube attached.

Bladder irrigations of various types were tried. All animals had solution G irrigations[7] at weekly intervals to prevent incrustations on the valve parts. Fortunately, the collection of urinary salts proved to be less troublesome than had been anticipated. Our longest period of observation was three months, and incrustations on the valve were negligible during this time.

It was soon determined that bladder irrigations with such solutions as silver nitrate, Zephiran, streptomycin, and sulfadiazine, encouraged rather



B.

A.

Fig. 2.—*A* and *B*, Views of bladder valve in place in the experimental animal. This valve was inserted one month before the photographs were taken.

than prevented urinary infection. Our best results were obtained when no irrigations were performed. This may be explained by the impossibility of keeping a protective covering over the end of the valve. The animals invariably removed the rubber protecting cap, which exposed the inside of the valve to contamination. It was impossible to clean the valve end, so that when the irrigating tube was secured in place unsterile material was probably forced into the bladder. The bladder remained free of infection when frequent irrigations were discontinued.

Bladder valves were inserted into twenty dogs. Two of the animals died as the result of anesthesia. Four animals developed perivesical abscesses following urethral division, and were sacrificed. Small urinary fistulas occurred in two animals, one beside the valve and the second through the wound. In the first animal the end of the valve became plugged with mucosa as a result of improper insertion into the bladder. Bladder drainage was established through a wound fistula. In the other animal the fistula was secondary to infection around the valve housing. Overwhelming cystitis with severe bladder spasm occurred in two animals and proved lethal in both instances.

Ten dogs did well and have been followed for periods up to three months. Periodic urine examination usually revealed two to four white blood cells per high power field in the unspun specimens. Retrograde pyelograms at three months in one animal outlined a normal upper urinary tract. Intravenous pyelograms in another animal, one month after division of the urethra, were within normal limits. The animals seemed comfortable on a twice daily drainage schedule, and remained in good health through the period of observation.

Autopsy demonstrated little gross tissue reaction to the valve. The abdominal wall fitted snugly around the valve housing and adhered firmly in the region of the projections. The tract around the nylon prosthesis was lined with glistening mucosa, which in most instances continued to the skin of the abdominal wall. This lining was continuous with the bladder mucosa, by both gross and microscopic examination. In some areas of the tract the mucosa was thinned out, while in others it was of normal thickness. Around the fistula there was little histologic evidence of an inflammatory reaction (Fig. 3). At necropsy, gross examination of the bladders exhibited minimal evidence of inflammation, with slight redness of the mucosa as the only consistent change. Microscopic sections taken through the bladder wall contained evidence of mild submucosal edema and congestion. Small areas of round-cell infiltration were occasionally observed. The mucosa remained intact throughout the bladder, even in areas adjacent to the valve (Fig. 4). Gross examination of the ureters and kidneys revealed no evidence of ascending infection, nor was dilatation of ureters or renal pelves noted. Microscopic examination of the upper urinary tract showed no abnormalities. From the autopsy findings it may be said that the creation of artificial urinary fistulas by means of nylon tubes is followed by only minimal reaction in the urinary tract and that such prostheses are well tolerated by the bladder and by the abdominal wall.

Recently it has been determined that the urethra can be as satisfactorily closed by ligature as by ligature and division. This does away with the

A. *B.* *C.*

Fig. 3.—*A*, Autopsy specimen with the valve tract laid open. Skin may be seen at the top of the picture and bladder at the bottom. The nylon valve has been removed and indentations made by the projections from the valve housing are clearly seen. Note that the tract is lined with tissue which is continuous with the bladder mucosa. *B* (×150), Sections through the tract at different levels. *C*, Note the transitional type of epithelium with which it is lined. On other sections this is seen to be continuous with the bladder mucosa. There is fibrosis beneath the mucosa but relatively little inflammatory reaction.

A.

B.

Fig. 4.—*A*, Post-mortem specimen of bladder six weeks following the implantation of a nylon valve unit. The valve tract was divided and may be seen at each side of the specimen. It is lined with a smooth layer of tissue which can be seen to be continuous with the bladder mucosa. The bladder is otherwise normal in appearance. The ureters are not dilated. *B* (×150), Section through the bladder wall. The mucosa is intact. There is slight edema, but very little inflammatory reaction.

source of infection which had resulted in the greatest percentage of failures in our experiments. An effective means of keeping the end of the valve sterile has been developed, by using a close-fitting finger cot filled with aqueous Zephiran 1:1,000 to cover it. Since these refinements have been introduced, no instance of severe bladder infection has been encountered.

SUMMARY

1. The need for effective control of urinary incontinence in children with myelomeningoceles is discussed.

2. A method is described for the insertion of a nylon prosthesis (which includes a valve) into the bladder through the abdominal wall, creating a urinary fistula which can be controlled.

3. Results of experiments on thirty-nine dogs are discussed.

4. Gross and microscopic examination of the urinary tract and the abdominal fistula demonstrate minimal inflammatory reaction to the valve housing.

5. This method for producing voluntary urinary control in laboratory animals has proved so encouraging that clinical trial of this procedure has been undertaken.

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THE ANATOMY OF THE NERVES SUPPLYING THE COMMON DUCT AND PROXIMAL DUODENUM

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THE detailed anatomy of the autonomic nerves in the region of the common bile duct and proximal duodenum has been investigated for many years. In a classic monograph, published in 1834, Swan[1] fully described and illustrated the abdominal distribution of the vagus and sympathetic nerves. Subsequently, his work has been confirmed by numerous authors.[2-9] Revival of interest in various types of nerve section for duodenal ulcer and biliary dyskinesia and in the laboratory investigation of these problems has stimulated workers to reassure themselves of the anatomic course and relations of the nerves supplying the stomach, duodenum, liver, biliary tract, and pancreas. This paper describes the anatomy of the autonomic nerves supplying the common bile duct and proximal duodenum, points out the importance of these structures in clinical and experimental studies, and recommends a more exact nomenclature than is in general use today.

MATERIALS AND METHODS

Dissections were made of 15 recently sacrificed dogs and 20 human cadavers obtained both as autopsy and fixed specimens. Vagus nerves were traced from the neck to their abdominal endings, and sympathetic trunks from the thorax to the celiac ganglia, and likewise further along their abdominal distribution. Particular attention was given to all nerves directed toward the biliary tract and proximal duodenum.

RESULTS

Our studies have confirmed the reports of others. There is little difference between man and the dog in the abdominal distribution of the autonomic nerves, and that difference is a quantitative one, for the size and number of nerve trunks in man are much greater.[4] Consequently, the findings of both groups are analyzed jointly for simplification (Table I and Figs. 1 to 5).

LEFT VAGUS (ANTERIOR GASTRIC NERVE)

Immediately upon emerging from below the diaphragm one or more branches of the left vagus nerve extend toward the right and, lying in the anterior layer of the gastrohepatic omentum, reach the porta hepatis. The major portion of these fibers, usually the largest of the branches, abruptly turns inferiorly along the common bile duct within the hepatoduodenal ligament and, after giving off filaments en route, reaches the proximal duodenum. The remainder of the left vagus fibers, those not directed toward the liver, then follow the lesser gastric curvature on its anterior surface, and the largest becomes the principal anterior nerve of the lesser curvature of Latarjet.[5]

Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 24-26, 1949.

TABLE I. AUTONOMIC NERVES TO BILIARY TRACT AND PROXIMAL DUODENUM

UNMIXED VAGUS FIBERS	MIXED VAGUS AND SYMPATHETIC FIBERS
(1) Constant trunk from left vagus direct to porta hepatis and thence to duodenum	(1) From right celiac ganglion; filaments from right dorsal chain, greater and lesser splanchnics, and both vagi
(2) Inconstant trunk from right vagus to common duct region	(2) From left celiac ganglion; filaments supply this ganglion as on right (1), and join right celiac ganglion via celiac plexus
	(3) Mixed nerve fibers accompanying celiac axis via hepatic artery

Branches regularly supply anterior gastric wall from fundus to pylorus and also anastomose with right vagus fibers but do not pass into duodenum. Moderate-sized filaments are distributed to the right celiac ganglion and smaller ones to the left. Others join the periarterial sympathetic trunks accompanying and branching with the celiac axis.

RIGHT VAGUS (POSTERIOR GASTRIC NERVE)

More often than not, the right vagus nerve pierces the diaphragm as a single trunk. It immediately divides into several equal-sized branches. One branch follows the lesser curvature of the stomach and is distributed to the posterior gastric wall in the same pattern as the left nerve anteriorly (principal posterior nerve of the lesser curvature).[5] There are connections or plexuses between the right and left nerves at the lesser curvature. Another branch from the main trunk, not constantly present, passes to the right through the posterior layer of the gastrohepatic omentum and supplies the common bile duct region. This trunk becomes unidentifiable in the nerve plexus around the common duct. Two other branches from the right vagus, of large caliber, occur constantly and run one to each side inferiorly and laterally, to fuse with the respective celiac ganglia. Some fibers are found along the celiac axis with the left nerve.

SYMPATHETIC NERVES

The sympathetic nerves are symmetrically arranged on the two sides and a description of one side only will be given. The dorsal chain and splanchnic trunks were followed from the chest to the level of the ipsilateral celiac ganglion. Whereas the dorsal chain usually sends a small branch to the ganglion, the greater and lesser splanchnics terminate in it, the greater merging with the upper portion and the lesser splanchnic with the lower or aorticorenal division of the ganglion. The least splanchnic is distributed to the renal plexus. The celiac ganglia, grossly similar to enlarged lymph nodes, are situated on the crura of the diaphragm at the level of the upper part of the first lumbar vertebra, one to either side of the midline, near the adrenal glands. By means of the celiac plexus the ganglia communicate freely across the midline.

COMMON PATHWAYS OF VAGUS AND SYMPATHETIC NERVES LEADING TO THE BILIARY TRACT AND PROXIMAL DUODENUM

Both celiac ganglia receive a large number of vagus fibers, preponderantly from the right vagus. There are abundant communications between the two

Fig. 1 (Dog 12).—Dissection to show left vagus distribution and mixed nerve pathways to the common duct region. *A*, Left vagus trunks in the thorax. *B*, Branch of left vagus direct to liver. *C*, Hepatic artery. *D*, Combined sympathetic and vagus trunks from right celiac ganglion en route to common bile duct region. *E*, Mixed nerve trunks in hepatoduodenal ligament, some of which are distributed to the wall of the proximal duodenum. *F*, Left vagus branches to right celiac ganglion and periarterial sympathetic filaments. *G*, Branch of right vagus to right celiac ganglion.

Fig. 2 (Dog 12).—Dissection of right vagus nerve to show branches to celiac ganglia. The stomach and spleen have been rotated mesially and the diaphragm cut away. *A*, Right vagus trunk from thorax. *B*, Branches of vagus merging with periarterial sympathetics. *C*, Left lumbar sympathetic chain. *D*, Left celiac ganglion. *E*, Branch from right vagus to left celiac ganglion. *F*, Branch from right vagus to right celiac ganglion.

Fig. 3 (Dog 3).—Dissection of autonomic nerves in the gastrohepatic and subhepatic areas. *A*, Left vagus nerve trunks at level of diaphragm. *B*, Branches of left vagus to porta hepatis. *C*, Left vagus branches in anterior layer of gastrohepatic omentum en route to celiac axis and right celiac ganglion. *D*, Right vagus branches in posterior layer of gastrohepatic omentum en route to celiac axis and right celiac ganglion. *E*, Combined vagus and sympathetic trunks from right celiac ganglion en route to biliary tract. *F*, Pylorus. *G*, Lesser gastric curvature. *H*, Cut edge of caudate lobe of liver.

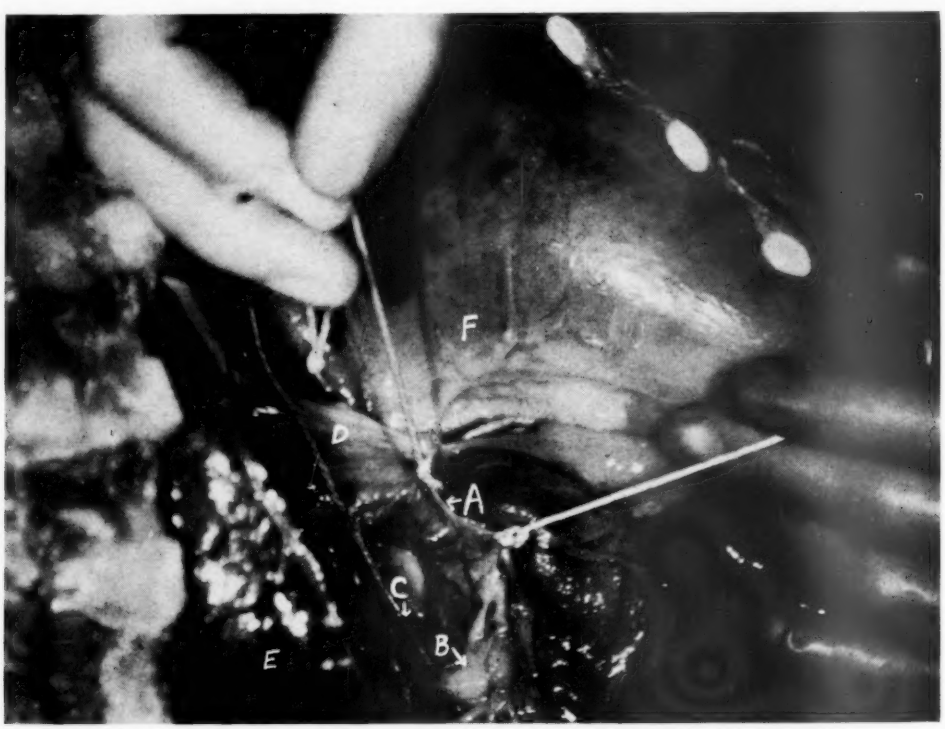

Fig. 4.—Human autopsy specimen, dissection to show connection between the right vagus nerve and right celiac ganglion. The stomach is retracted to the left. *A*, Branch from right vagus merging with right celiac ganglion and celiac plexus fibers. *B*, Right celiac ganglion. *C*, Lumbar sympathetic chain. *D*, Reflected hepatoduodenal ligament and contained structures. *E*, Right iobe of liver. *F*, Lesser curvature of stomach.

ganglia (celiac plexus). Emerging from the right celiac ganglion are several large nerve trunks which accompany the hepatic artery. These trunks are joined by vagus fibers traveling with periarterial sympathetics from the celiac artery region and are directed toward the common bile duct along the hepatic artery. As they approach this structure, some filaments branch directly to the duct area and others anastomose to form a plexus. Within the hepatoduodenal ligament there are further anastomoses and branching, not only with respect to the fibers from the celiac ganglion but also between these and the "pure" fibers direct from the left vagus.

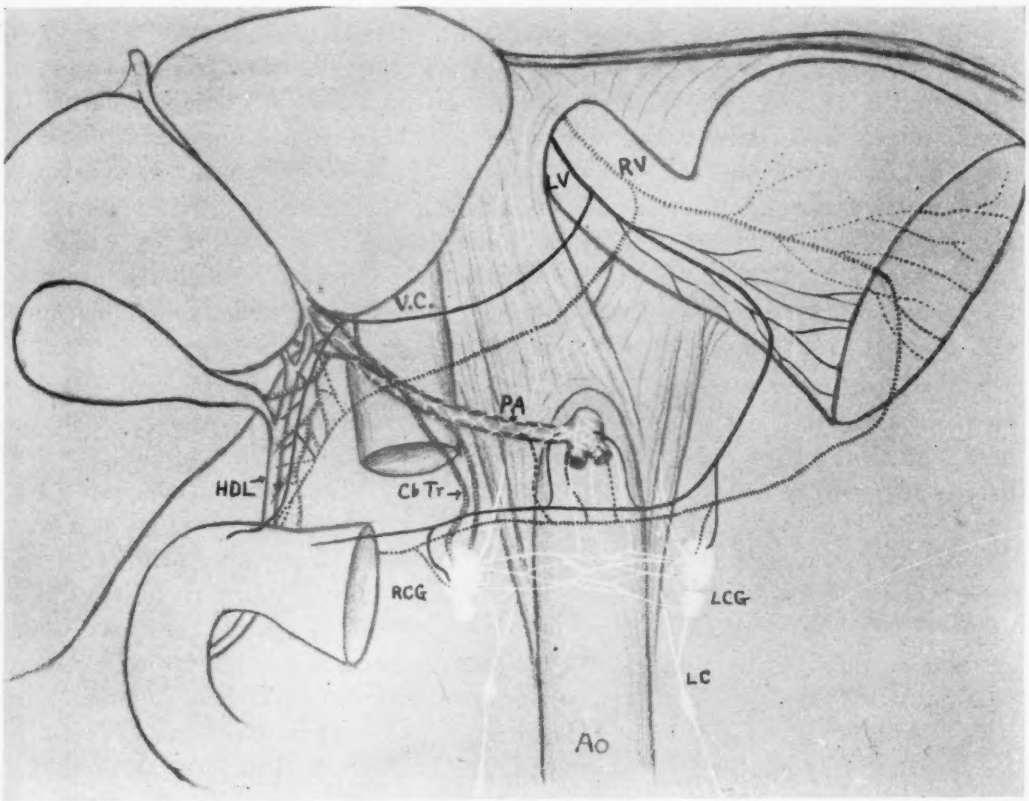

Fig. 5.—Diagrammatic sketch of the major pathways of the vagus and sympathetic systems in the upper abdomen. *VC*, Inferior vena cava. *AO*, Abdominal aorta. *LV*, Left vagus nerve at diaphragm. *RV*, Right vagus nerve at diaphragm. *LCG*, Left celiac ganglion receiving greater and lesser splanchnics from above and a branch from the lumbar chain. *RCG*, Right celiac ganglion with connections as on left, ganglia joined by filaments of celiac plexus. *PA*, Periarterial sympathetics of hepatic artery. *CbTr*, Combined trunks of vagus and sympathetic fibers from right celiac ganglion en route to bilary tract via hepatic artery. *HDL*, Hepatoduodenal ligament area containing anastomosing nerve trunks.

In summary, the autonomic nerves supplying the biliary tract and proximal duodenum are as follows (Table I and Figs. 1 to 5):

1. *Unmixed Vagal Fibers.*—The sources of these fibers are the constant branches of the left vagus to the porta hepatis and an inconstant one from the same nerve crossing directly through the anterior leaf of the gastrohepatic omentum to the lower portion of the biliary tract.

2. *Mixed Vagus and Sympathetic Fibers.*—These make up by far the greater part of the autonomic nerve supply to this area. They arise from both

celiac ganglia (the right and left ganglia are joined by the celiac plexus) and reach the common duct region along the hepatic artery and via the hepatoduodenal ligament. The components of this mixture are chiefly filaments from the right vagus, with a small number of left vagus fibers combined with large numbers of sympathetic fibers from the dorsal chains and greater and lesser splanchnic nerves, and filaments direct from both vagi that merge with periarterial sympathetics along the celiac axis.

DISCUSSION

The exact pathways taken by vagus fibers after uniting with sympathetic trunks have remained an unsolved problem. In man it is assumed that, since branches from both vagi enter both celiac ganglia, the outflow from the ganglia is composed of both sympathetic and parasympathetic fibers. By means of degeneration experiments this condition has been found by Alexander[7] to exist in the cat. Since vagus fibers accompany the periarterial sympathetics of the celiac axis and its branches and also all the branches leaving the celiac ganglia and celiac plexus, it is readily seen that the majority of the trunks in the gastroduodenal-subhepatic region consists of a mixture of autonomic nerves. The vagus fibers proceeding directly to the biliary tract and duodenum represent a small proportion of total vagus fibers.

The clinical significance of the complex nerve pattern concerns surgical operations for upper abdominal pain, especially biliary dyskinesia. As in the past,[10] surgeons have continued to section nerve trunks in the upper abdomen in the hope of relieving abdominal pain.[8, 9, 11-14] These operations have frequently been combined with celiac ganglionectomy or sympathectomy at higher levels. Since the sympathetics carry afferent pain fibers, sympathectomy has been employed as a method for relief of abdominal pain of biliary tract origin.[15] If the sympathectomy includes extirpation of one or both celiac ganglia, as reported by Grimson,[14] then there is necessary interruption of many vagus fibers. This produces section of mixed nerves, with dual function, and it is difficult in analyzing the result to say whether pain relief was effected by the cutting of sympathetic or parasympathetic nerves. Regeneration of nerves after section in the hepatoduodenal ligament has been reported.[13] Splanchnicectomy and celiac ganglionectomy must be done for complete sympathetic nerve interruption.

In operations designed to section vagus trunks in the gastrohepatic omentum, as recently described by Jackson,[9] not only may sympathetic fibers be cut, but only a small percentage of the total vagus fibers would be included in the designated area. The theory that overactive vagal impulses may cause postcholecystectomy pain, an idea originally proposed by Oddi,[16] has been clinically tested by Crile,[17] who obtained relief in two patients by subdiaphragmatic vagotomy. The success of this procedure is to be taken as clinical evidence of the role of the vagus in producing biliary tract pain in certain patients. It also points out the necessity of performing complete vagotomy at the diaphragmatic level rather than random sectioning of vagus branches at lower levels.

Experimentally, electrical stimulation or ablation of upper abdominal autonomic nerves has often been done to note the effect on function of abdominal viscera. Many of these experiments were carried out in the apparent belief that a "pure" sympathetic nerve group existed, whereas both vagus and sympathetic nerve elements were present.

Although the nomenclature describing the nerves in the gastrohepatic omentum and hepatoduodenal ligament should indicate their sympathetic and parasympathetic components, earlier authors and a few modern workers in this field have perpetuated terms which imply true anatomic and physiologic entities where none is known definitely to exist. Examples are "nerf pancreaticocholedocien,"[4] "gastroduodenal nerve,"[18] and "nervi choledochi et pancreatici."[8] Since the majority of nerves in the hepatoduodenal ligament are composed of sympathetic and parasympathetic fibers, and since the direct vagus branches anastomose freely with them, it is impossible to isolate a single nerve trunk that could be called a "pure" nerve, with the exception of the two vagus branches mentioned previously. For clarification it is recommended that the various combined branches to the biliary tract and proximal duodenum be called "autonomic nerves" or "mixed sympathetic and vagus nerves."

SUMMARY

1. Dissections of the vagus and sympathetic nerves supplying the biliary tract and proximal duodenum have been done in 15 dogs and 20 human cadavers. The results confirm previous work of others, and the following points are emphasized:

(a) With the exception of two branches coming directly from the vagi, the sympathetic and parasympathetic nerves follow common pathways in their course to the biliary tract and proximal duodenum.

(b) There is free anastomosis between the right- and left-sided nerve trunks of both systems.

(c) Interruption of vagus nerve fibers must be done at the diaphragmatic level; in the case of the sympathetics, the splanchnics, celiac ganglia, and possibly the dorsal chains must be severed or ablated.

2. In operations for upper abdominal pain, especially biliary dyskinesia, the ineffectiveness of random sectioning of vagus nerve trunks in the subhepatic area is demonstrated.

3. Operations upon the sympathetic system in the upper abdomen, both for clinical and experimental purposes, are necessarily accompanied by interruption of some vagus fibers, and the results should be so interpreted.

4. Recommendation is made to clarify the current nomenclature by replacing descriptive terms such as "nervi choledochi et pancreatici" with other terms which denote their sympathetic and parasympathetic components, such as "autonomic nerves" or "mixed sympathetic and vagus nerves" to the biliary tract and proximal duodenum.

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EFFECTS OF A NEW QUATERNARY AMINE AND A NEW IMIDAZOLINE DERIVATIVE ON THE AUTONOMIC NERVOUS SYSTEM

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NUMEROUS new drugs acting upon the sympathetic and parasympathetic divisions of the autonomic nervous system have been investigated during recent years. Some of these drugs block adrenergic neuro-effector organ transmission, others cholinergic neuro-effector organ transmission, and a few block cholinergic transmission occurring in autonomic ganglia. Examples of newer drugs blocking sympathetic nerve transmission at the effector organ are Priscol,[1] F 933, a Benzodioxane derivative,[2, 3] and Dibenamine.[4] An ester of acetyl choline, Dibutoline,[5] has been used to block cholinergic pathways. The tetraethylammonium ion, according to Acheson and Moe,[6] prevents transmission of impulses through autonomic ganglia. Literature concerning actions of older drugs, picrotoxin, nicotine, curare, atropine, ergotoxin, yohimbine, ergotamine tartrate, F 883, etc., have been described in a separate report.[7]

Two new compounds, one a ganglionic blocking agent and the other an adrenolytic or sympatholytic drug, have been investigated and are both reported in this paper; similarities of effect upon functions of the autonomic nervous system are presented and differences contrasted.

The first of these new compounds is 2,6 dimethyl, diethyl piperidinium bromide,† referred to in this report as SC 1950. It was demonstrated that it blocks transmission through autonomic ganglia in the experimental animal, this action being five to seven times as potent as that of tetraethylammonium chloride or Etamon. In unanesthetized dogs it reduced intestinal tone and contractility and in large doses (20 to 25 mg. per kilogram) produced a flaccid curare-like paralysis with respiratory death.[8] Our previous studies[9] have in general confirmed this observation in animals and indicated similar effects in man.

The second of these drugs, 2(N, p-tolyl-N (m′ hydroxyphenyl)-aminoethyl)-imidazoline hydrochloride, hereinafter called C 7337, has been shown by Meier and Yonkman[10] to be a potent adrenolytic agent. Unlike Priscol, however, it had no cholinergic effects such as myotropic contractile activity in the experimental animal. This drug was effective by both parenteral and oral administration in animals.

Supplies of SC 1950 and a grant in aid given by the Research Laboratories of G. D. Searle & Co., Chicago, Ill.

Supplies of C 7337 and a grant in aid given by Ciba Pharmaceutical Products, Inc., Summit, N. J.

Aided in part by a grant from the American Foundation for High Blood Pressure.

Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 24-26, 1949.

*U. S. Public Health Research Fellow in Surgery.

†Synthesized by the research laboratories of G. D. Searle, Inc.

Experiments undertaken in this laboratory first evaluated the effects of SC 1950 and of C 7337 upon the circulatory system and gastrointestinal tract of dog and then extended to include trial and testing in man.

ACTION OF SC 1950 AND C 7337 IN THE DOG

Method

Acute Experiments.—Dogs weighing 9 to 16 kilograms were anesthetized using intravenous chloralose, 0.1 Gm. per kilogram. A tracheal cannula was inserted, the carotid arteries isolated, and the vagi divided. A left lumbar sympathectomy was performed transperitoneally. The right femoral artery was divided and cannulated proximally and distally; the left was also divided and then ligated proximally and cannulated distally. This permitted recording of three blood pressures, using a mercury manometer connected to the proximal cannula in the right femoral artery to record mean systemic blood pressure, and the two connected to the distal segments for measuring back pressure in the femoral arteries. Respirations were measured by a pneumograph connected to a recording tambour.

After preparation, standard tests of the circulatory system were employed in each animal. Carotid sinus reflexes were elicited by occlusion of both common carotid arteries using bulldog clamps applied for one minute. Peripheral vagal stimulation was accomplished for 15 seconds using a tetanizing current from a Harvard inductorium set at 7 or 8 cm. Central vagal stimulation also employed a tetanizing current for 15 seconds but the setting of the inductorium was reduced to 6 or 7 cm. Epinephrine was injected as a 1:10,000 solution through a venous cannula. Neostigmine methylsulfate and pituitrin were also given intravenously.

These tests were each employed before use of one or the other of the two new drugs. SC 1950 was injected intravenously in doses of 0.5 to 20 mg. per kilogram or C 7337 in doses of 0.02 to 5.0 mg. per kilogram. The new drug employed for the acute experiment was administered several times to the same animal, often using larger amounts during subsequent injections. Tests were performed before and after the initial injection of the new drug and following each subsequent injection.

Experiments Employing Increased Intracranial Pressure.—Dogs were anesthetized using chloralose, 0.1 Gm. per kilogram, a trachea cannula was inserted, blood pressure was recorded from a femoral artery, and respirations were recorded. The two cervical vagus trunks were divided. A small area of the parietal bone was exposed through a small incision. Through this bone a special trocar was inserted and connected by rubber tubing with a mercury manometer and a pressure bottle filled with saline solution. Carotid sinus reflexes were repeated at intervals during ½ to 1 hour of continuous recording of blood pressure and respiration. Either of the test drugs employed was given early during this observation period and repeated if necessary until reduction of blood pressure and block of the carotid sinus reflex occurred. Pressure within the skull was then increased by forcing saline solution through the trocar in the skull. Intracranial pressure was constantly kept above mean systolic blood pressure until death occurred.

Experiments in Unanesthetized Trained Dogs.—Each new drug was given to trained unanesthetized dogs. Blood pressures were obtained before and at intervals during several hours following injection of the drug. Pulse rates were also counted. Each drug was tested using normal dogs and also using dogs made hypertensive three months to one year previously by bilateral excision of the carotid sinuses, division of one vagus trunk in the neck, and division of the depressor fibers of the other vagus trunk.

Each new drug was also given to trained, normal, unanesthetized animals after fasting 12 hours. A stomach tube was passed ten minutes after injection of drug and through it 30 Gm. of barium sulfate in 100 c.c. aqueous suspension were administered. The tube was withdrawn and the gastrointestinal tract immediately observed fluoroscopically. Gastric activity was noted and the interval between administration of barium and initial emptying into the duodenum was accurately timed. Roentgenograms were obtained ½ and 1 hour after administration of barium and subsequently at hourly intervals until 6 hours had elapsed.

Control Observations

Acute Experiments.—Changes of blood pressure, pulse rate, respirations, and back pressure in the divided femoral artery of a normally innervated and a sympathectomized hind limb occurring with occlusion of both carotid arteries; central or peripheral stimulation of one vagus; and injection of epinephrine, neostigmine, or pituitrin are commonly known and details of several complete control experiments will be omitted. Rather results of the individual tests before administration of the new drug in each acute experiment will be referred later as effects of the drug are presented.

Experiments Employing Increased Intracranial Pressure.—Increased intracranial pressure in normal dogs produced elevations of systemic blood pressure consistently over 200 mm. Hg and occasionally approaching 300 mm. Hg. Graded hemorrhage or histamine infusion sufficient to reduce blood pressure below 80 mm. Hg for ½ to 1 hour variably reduced but did not prevent rise of systemic blood pressure with increased intracranial pressure.

Experiments in Unanesthetized Trained Dogs.—Blood pressures and pulse rates of normal or neurogenic hypertensive dogs taken at hourly intervals fluctuated moderately. Spontaneous marked reduction of blood pressure was not observed.

Fluoroscopic examinations and subsequent roentgenograms in eleven animals revealed that normally or without drugs, gastric peristalsis was active. Emptying of barium into the duodenum began in from less than 1 minute to slightly less than 8 minutes. Average time of initial emptying was 4.1 minutes. Time required for emptying of barium from the stomach varied markedly in a few animals, but in most animals emptying times were similar. Average amount of emptying at ½ hour was 30 per cent, at 1 hour 46 per cent, and at two hours 84 per cent. Gastric emptying was complete at 3 hours in eight of ten dogs. Of 9 dogs in which observations could be made with accuracy, the first of the barium had traveled through the ileum and reached the colon at 2 hours in three dogs, and at 3 hours in six dogs.

Observations Employing SC 1950

Acute Experiments.—Acute experiments with SC 1950 were carried out in seven dogs using twenty-three injections of the drug. Initial mean systolic blood pressure of the anesthetized prepared animals varied from 80 to 120 mm. Hg. With three exceptions SC 1950 in dose ranges of 0.05 to 20 mg. per kilogram consistently lowered blood pressure. With doses of 0.05 to 1.0 mg. per kilogram, reduction of pressure was moderate, lasting only 2 to 5 minutes. As dose increased, the depression of blood pressure became more pronounced and duration of depression lengthened. Doses of 5 to 20 mg. per kilogram reduced blood pressure to one-half or one-third the level before injection, and depression persisted 25 to 50 minutes. Small doses did not affect heart rate, but 5 to 20 mg. per kilogram produced cardiac slowing from an average rate of 159 per minute to an average of 93 per minute. This bradycardia persisted as long as did depression of blood pressure.

Doses of 0.02 to 1.0 mg. per kilogram SC 1950 in three animals did not prevent vascular reflexes. In four animals receiving 5 to 20 mg. per kilogram SC 1950 per injection, the rise of blood pressure normally occurring in response to occlusion of the carotid arteries was uniformly prevented in each of ten test periods. The rise of blood pressure occurring with faradic stimulation of the proximal divided vagus was prevented in three dogs and reduced in the fourth. Fall of blood pressure and cardiac slowing normally occurring with faradic stimulation of the distal divided vagus were blocked with one single exception following 5 to 20 mg. per kilogram of SC 1950. In this exception blood pressure and pulse rate were reduced by peripheral vagal stimulation after 5 mg. per kilogram but after an additional 10 mg. per kilogram were not affected.

Blood pressure measured by cannulae in the distal ends of the divided femoral arteries, representing "back pressure" or, indirectly, peripheral resistance, was lower in the sympathectomized extremity and responded slowly or passively in this limb during reflexes before the drug. Following SC 1950, peripheral or back pressure in the normal extremity decreased to equal that in the sympathectomized limb, and responses to cardiovascular reflexes were equally slow and passive.

Epinephrine, two to four gamma per kilogram injected intravenously, normally produced blood pressure increases ranging from 30 to 56 mm. Hg, following which blood pressure returned to pre-injection levels in two minutes or less. After administration of 5 to 10 mg. per kilogram of SC 1950 the response to epinephrine was enhanced, pressures rising 46 to 168 mm. Hg, a response two to four times as great as that before SC 1950. The duration of the pressor response was increased to 3.5 to 7 minutes. The initial decrease of back pressure usually occurring in the normal leg following epinephrine was prevented by SC 1950, the response then being similar to that in the sympathectomized extremity.

In four instances 0.5 to 1.0 mg. neostigmine methylsulfate was administered intravenously following SC 1950; in each case pressure rose to levels near those before SC 1950 and vascular reflexes again became active.

SC 1950, 5 mg. per kilogram, was administered intravenously to seven dogs under ether anesthesia undergoing major abdominal surgery in the course of another research problem. Immediate cessation of respirations occurred in each of these animals. Three died of respiratory failure in spite of attempts at resuscitation. Four recovered after artificial respiration given for 3 to 5 minutes.

Experiments Employing Increased Intracranial Pressure.—Doses of SC 1950 varying from 5 to 15 mg. per kilogram intravenously were sufficient to prevent rise of blood pressure with carotid sinus reflexes and reduce blood pressure, but did not prevent marked increase of systemic blood pressure in response to increased intracranial pressure in three dogs. It reduced this response partially in a fourth dog given 15 mg. per kilogram intravenously. Increases of blood pressure during increase of intracranial pressure after SC 1950 were respectively 58 to 218, 100 to 280, 54 to 204, and 40 to 98.

Experiments in Unanesthetized Trained Dogs.—Doses of 2 to 15 mg. per kilogram of SC 1950 given normal unanesthetized dogs produced pressor responses in eleven of twelve animals, average blood pressure before drug being 126 mm. Hg and afterward 147 mm. Hg. One dog had an immediate depressor response, pressure falling from 126 mm. Hg to 104 mm. Hg, and two others had an immediate rise of blood pressure followed by a fall to levels below normal. Pulse rates increased from an average of 88 per minute to an average of 142 per minute. In eleven tests on neurogenic hypertensive dogs there was a consistent lowering of blood pressure and slowing of pulse. Doses of 2 to 10 mg. per kilogram SC 1950 lowered pressures from an average of 223 mm. Hg to an average of 127 mm. Hg, with this reduction persisting 30 to 230 minutes. Pulse rates before the drug averaged 180, afterward 114.

Effect of SC 1950 on the gastrointestinal tracts of eleven normal trained dogs was studied. Doses of 0.4 to 1.0 mg. per kilogram, which are arbitrarily considered small, caused rapid initial emptying, this usually occurring in one or two minutes. Similarly, rate of emptying was increased as compared with normal dogs, the stomach having passed 60 to 80 per cent of barium into the small intestine at ½ hour in four of the five dogs and 90 to 100 per cent of barium within 1 or 2 hours. Barium reached the colon in two or three hours. Larger doses, 5 to 10 mg. per kilogram, conversely effected marked delay of gastric emptying and of small intestine transit time. Initial emptying time averaged 29 minutes. The stomach had passed no barium in five dogs and only 20 per cent in the sixth at ½ hour and required 3 to 6 hours to pass 80 per cent or more. Barium reached the colon only after 3 to 6 hours, transit time in the ileum being rapid as the drug effect wore off and gastric emptying occurred.

Observations Employing C 7337

Acute Experiments.—Acute experiments with C 7337 were carried out on four dogs using thirty injections of drug. Initial mean systolic blood pressure of the anesthetized prepared animals ranged from 110 to 138 mm. Hg. Intravenous injection of 0.02 to 5 mg. per kilogram consistently produced decrease of systemic blood pressure. Duration of depression and degree of depression seemed directly proportional to amount of drug injected. With 0.02 to 0.05 mg. per kilogram, pressure was lowered slightly to 75 to 90 per cent of the level be-

fore injection, and returned to pre-injection levels after 5 to 8 minutes. With initial dose of 0.4 mg. per kilogram or more, pressure fell to less than one-half the pre-injection level and remained depressed for as long as two hours. Following repeated injections in two dogs an initial slight rise of pressure (not over 10 mm. Hg) preceded its depression, lasting 2 to 3 minutes in each instance. Pulse rate was increased by C 7337 in all dose ranges from an average of 171 before drug to an average of 204 after first injection.

Carotid sinus reflexes were active before drug in all dogs. Injection of 0.02 mg. per kilogram reduced the pressor response to bilateral carotid occlusion, and doses of 0.05 to 5 mg. per kilogram either prevented this rise of pressure completely or markedly reduced the rise. Doses of 0.2 mg. per kilogram or more reduced or prevented the pressor response normally occurring with faradic stimulation of the proximal end of the divided vagus in each thirteen tests. The fall of blood pressure and slowing of cardiac rate normally occurring in response to peripheral vagal stimulation was not affected by C 7337 in seventeen experiments.

The pressures measured in the distal ends of the divided femoral arteries were reduced by C 7337, and after the drug, pressure in the normal leg approximately equaled that in the sympathectomized leg, and responded more passively to vascular reflexes than before drug, thus resembling the sympathectomized extremity.

Following doses as small as 0.02 mg. per kilogram C 7337, the pressor response to intravenous epinephrine, 3 to 4 gamma per kilogram was markedly reduced. Following repeated injections of C 7337 or after injection of large doses there was a depressor response to injection of epinephrine. This effect was consistent in all experiments. A typical recording of an acute experiment illustrating adrenalin blockade is presented in Fig. 1.

Two animals were given 1.0 mg. neostigmine methylsulfate following C 7337. There was no rise of pressure or other noted effect. In three cases surgical pituitrin, 20 units intravenously, caused a rise of pressure with partial reactivation of vascular reflexes.

Experiments Employing Increased Intracranial Pressure.—Doses of C 7337 varying from 2 to 15 mg. per kilogram were sufficient to prevent rise of blood pressure with bilateral carotid occlusion and to reduce systemic blood pressure. They were also sufficient to decrease or prevent completely increase of systemic blood pressure during increased intracranial pressure in five dogs. A sixth dog tested after receiving only 2 mg. per kilogram had a normal increase of blood pressure with this test, pressure rising from 102 to 200 mm. Hg. Pressures in the other five dogs changed during this test from 86 to 168, 58 to 98, and 74 to 100 in three, death occurring in the remaining two with prompt decrease of blood pressure without preliminary rise.

A comparison of the effects of SC 1950 and C 7337 on the anesthetized dog is seen in Table I.

Experiments in Unanesthetized Trained Dogs.—C 7337 was administered orally, intravenously, and intramuscularly to normal dogs in seventeen experiments and to dogs with neurogenic hypertension in twenty-nine experiments.

Dosages used were from 0.5 to 2.0 mg. per kilogram parenterally, and 2.0 and 5.0 mg. per kilogram orally. Of seventeen tests in normotensive dogs receiving C 7337, thirteen had a reduction of pressure from an average of 126 mm. Hg to an average of 101 mm. Hg. Duration of depressor action in these dogs averaged 45 minutes after intravenous injection, 130 minutes following oral administration, and 165 minutes when given intramuscularly. Twenty-six of twenty-nine tests in neurogenic hypertensive dogs showed reduction of pressure from an average of 199 mm. Hg before drug to an average lowest pressure of 111 mm.

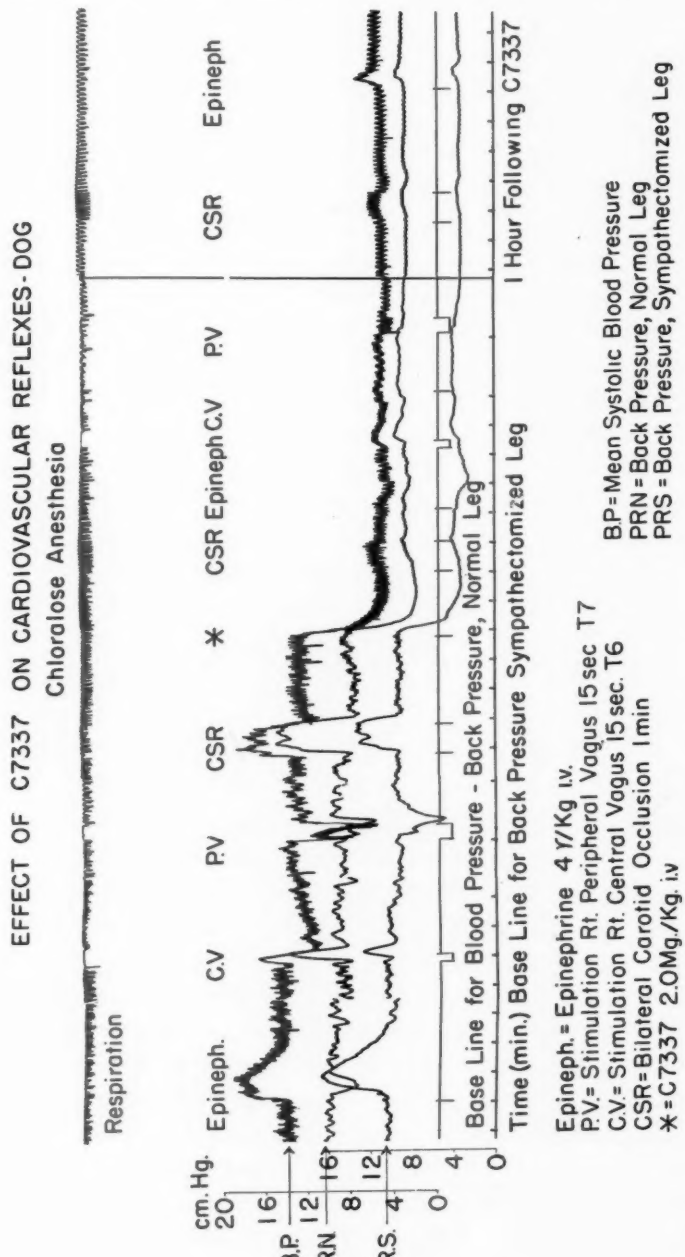

Fig. 1.—A composite record demonstrating effect of intravenously administered C 7337 on standard cardiovascular reflexes of the dog. Chloralose anesthesia was used.

TABLE I. A COMPARISON OF EFFECTS OF SC 1950 AND C 7337 IN DOGS ANESTHETIZED WITH CHLORALOSE*

BOTH DRUGS	
Lower blood pressure	
Block carotid sinus reflexes	
Block reflexes to central vagal stimulation	
Make reflex responses of back pressure in normal extremity like that in sympathectomized extremity	
SC 1950	C 7337
Blocks reflexes to stimulation of peripheral vagus	Does not block reflexes to stimulation of peripheral vagus
Slows pulse	Produces tachycardia
Accentuates action of epinephrine	Blocks pressor effect of epinephrine
Is reversed by neostigmine	Is not affected by neostigmine
Does not prevent hypertension occurring with increased intracranial pressure	In large doses prevents hypertension with increased intracranial pressure

*Each dog received only one drug, administered intravenously.

Hg afterward. Average duration of the period of depression of pressure was 67 minutes following intravenous administration, 148 following oral administration, and 173 minutes following intramuscular injection. Pulse rates were increased in eleven of the thirteen tests in normal dogs with reduction of pressure and in eighteen of the twenty-six tests in hypertensive dogs having reduction of pressure after C 7337.

Effect of C 7337 on the gastrointestinal tracts of six normal trained dogs was studied using 1.5 mg. per kilogram intravenously. Initial emptying of the stomach occurred in from 3 to 5 minutes in four, and was apparently delayed in two, being 12 and 19 minutes. All barium had passed from the stomach of one dog at 1 hour and of another at 2 hours. Completion of emptying of the stomach of the other four dogs occurred in 3 to 6 hours as in the control animals. In all six the first barium reached the colon in 2 to 3 hours as in dogs without medication.

EFFECT OF SC 1950 AND C 7337 ON MAN

Sixty patients were given doses of SC 1950 varying from 0.5 to 2.0 mg. per kilogram parenterally without ill effects. Oral administration to six patients of 2 to 15 mg. per kilogram (100 to 900 mg. total dose) of SC 1950 produced only slight or inconsistent effects. Forty-one patients were given C 7337 intravenously, and an additional thirty-six patients received it orally. Of these, thirty received repeated oral doses every 2, 3, or usually every 4 hours during treatment periods varying from 1 to 2 days to 4 months. Dose ranges using C 7337 have been 0.5 to 2.0 mg. per kilogram intravenously or orally since the drug has been as effective orally as parenterally. Either drug was effective within a few minutes of intravenous injection. Subjective symptoms following administration were similar. There was an immediate general feeling of warmth with some reddening of the skin. With SC 1950 slight palpitation was occasionally described. Following intravenous injection of C 7337, an immediate marked increase of heart rate was noted which often annoyed the patient. Within a few minutes of injection of SC 1950 dilatation of pupils, loss of accommodation, and dryness

of the mucous membranes occurred. These effects did not occur following C 7337. Either drug occasionally caused ptosis of eyelids and engorgement of conjunctival blood vessels. C 7337 caused nasal congestion resembling that occurring after bilateral upper thoracic sympathectomy. These changes persisted for 30 to 60 minutes after intravenous injection of either drug. Intramuscular injection produced effects within 20 to 30 minutes which persisted 2 or 3 hours. Oral administration of C 7337 produced subjective changes in 30 to 40 minutes which persisted for 2 or 3 hours. After repeated oral doses symptoms became less noticeable and less objectionable. Urinalyses, red blood cell counts, and differential white blood cell counts were performed on most patients tested and all treated several weeks or more. No significant abnormalities were noted.

Effects Upon the Cardiovascular System

SC 1950.—With the exception of one patient who had slight pressor responses with repeated doses of SC 1950, lowering of blood pressure was consistently produced by 0.5 to 1.5 mg. per kilogram. The lowering of blood pressure readings obtained with the patient supine was more marked in hypertensive patients than in normotensives, average reduction being from 190/130 to 114/80 in the former and from 125/77 to 94/62 in the latter. Maximum fall occurred within 2 minutes of intravenous injection. Pressure then gradually rose to reach its former levels in 10 to 120 minutes. Duration of the depression varied according to the dose of the drug and also from patient to patient, but usually it persisted about ½ hour. Reduction of blood pressure with standing was more pronounced and persisted for ½ hour or longer after return of supine pressures to control levels. Cardiac rate was not markedly affected but most patients had a slight tachycardia during the hypotensive effect of the drug.

Pressor responses normally occurring with immersion of hand in ice water for 60 seconds were tested before and after SC 1950 in fourteen patients. In each a pressor response was obtained before the drug. After 1.0 to 1.5 mg. per kilogram this pressor response to ice water was prevented or reversed in eleven cases, reduced in two, and remained active in one. A pressor response was also obtained in each of sixteen patients before SC 1950 with prolonged breath holding in expiration. This response was prevented or reversed in twelve patients receiving 1.0 to 1.5 mg. per kilogram SC 1950 and reduced in the other four.

Six patients received 0.6 to 1.0 mg. of neostigmine methylsulfate intravenously during the hypotensive effect of SC 1950. Changes of blood pressure and pulse rate and block of pressor response to ice water and breath holding existing after the SC 1950 also persisted after the neostigmine methylsulfate. Time of return to normal after both drugs did not seem to differ from the expected time of return after SC 1950 alone.

Temperature gradients of lower extremities exposed at a constant room temperature of 25° C. were measured using a Cambridge thermocouple. Normally temperatures of the toes were several degrees lower than those of the umbilicus. This gradient was completely abolished, toes warming to equal temperature at the umbilicus, in nine of twelve patients receiving SC 1950, 1.0 to 2.0

mg. per kilogram intravenously. Two of the twelve patients had marked arteriosclerotic occlusive vascular disease; in one there was no change of gradient and in the other the gradient was reduced. The remaining patient had a total dose of only 66 mg. SC 1950 and had no change of gradient.

C 7337.—Twelve hypertensive patients received 1.0 to 1.5 mg. per kilogram of C 7337 intravenously. Average blood pressure with patients supine before C 7337 was 188/166. Afterward pressure was reduced in all twelve patients. Average lowest pressure following drug was 148/99. An additional patient had persistent hypertension following bilateral total thoracic and partial lumbar sympathectomy, splanchnicectomy, and celiac ganglionectomy and had no reduction of pressure with C 7337. Eleven normotensive patients were given 1.0 to 1.5 mg. per kilogram of C 7337 intravenously. Eight had a fall of pressure from an average of 123/79 to 97/52. Blood pressure was not reduced in the remaining three. Effect on pulse rate was consistent, all patients having a more rapid rate after the drug. Average pulse rates of hypertensive and normal patients before the drug were, respectively, 78 and 81 and afterward were 112 and 129. With standing, blood pressure decreased in all patients and there was a further increase of cardiac rate.

Pressor responses occurring with immersion of one hand in ice water were tested before and after C 7337 in 14 patients, in 13 of whom pressor responses were obtained before drug. Following C 7337 this response was prevented or markedly reduced in five patients, was somewhat diminished in two, and occurred as before the drug in seven. A pressor response with prolonged breath holding was obtained in eight of fourteen patients before drug. Following C 7337 in these eight patients the pressor response was prevented in one, decreased in two, and occurred as before the drug in five.

Skin temperature gradients were measured in twenty-seven patients. The normal gradient of the exposed lower extremities was completely abolished in eighteen of the twenty-seven patients, toe temperature equaling temperature at the umbilicus, and markedly reduced in two others. The block of temperature gradient produced lasted from 1 to 3 hours. Among the remaining seven patients, one with severe Buerger's disease in the left leg had a block of gradient in the right leg but no change in the left. Five with advanced arteriosclerotic occlusive disease and one with severe Raynaud's disease had no warming of extremities or loss of gradient. Two of the arteriosclerotic patients with no change of gradient following C 7337 had lumbar sympathectomies performed later, and in neither was skin temperature gradient improved postoperatively.

Since many of the patients tested with C 7337 had some form of vascular disease, electrocardiograms were obtained in each before administration of drug. C 7337 was not given to patients with a history suggestive of anginal type pain or with significant abnormalities in their electrocardiograms. Nevertheless, three patients receiving 1.0, 1.2, and 1.5 mg. per kilogram, respectively, intravenously and having reduction of blood pressure experienced substernal pain lasting 2 to 3 minutes. This pain was relieved by nasal oxygen. Subsequent electrocardiograms a few days later revealed no abnormalities.

Effects Upon the Gastrointestinal Tract

SC 1950.—Gastrometric and intubation balloon studies of the small intestine were performed in 20 patients. Three hundred cubic centimeter balloons were used in the gastrometric studies of the fasting stomach. They were placed in the fundus and mid-stomach under fluoroscopic guidance and connected to a recording bromoform manometer. Twenty cubic centimeter balloons, one on a Miller-Abbot tube, or 4, eight inches apart on a four lumen tube (Chapman, Stanbury and Jones[11]), were employed to determine effects upon the motility of the small intestine.

Administration of 1.0 to 1.5 mg. per kilogram of SC 1950 intravenously consistently caused decrease of resting intralumenal pressure or "tone" and of forceful fluctuations of pressure of "peristalsis" in both the stomach and small intestine. Gastric tone began rising 25 to 40 minutes following SC 1950 and after 60 to 80 minutes was often slightly greater than before the drug (Fig. 2). Peristaltic activity ceased in the stomach for 30 minutes or more in all cases, an average of 58 minutes elapsing before return of contraction waves. In the small intestine decrease of tone and absence of contraction waves persisted somewhat longer than in the stomach. In the small intestine normal contractions appeared within a few minutes of resumption of activity, but gastric contractions were reduced for 30 minutes or more after their return.

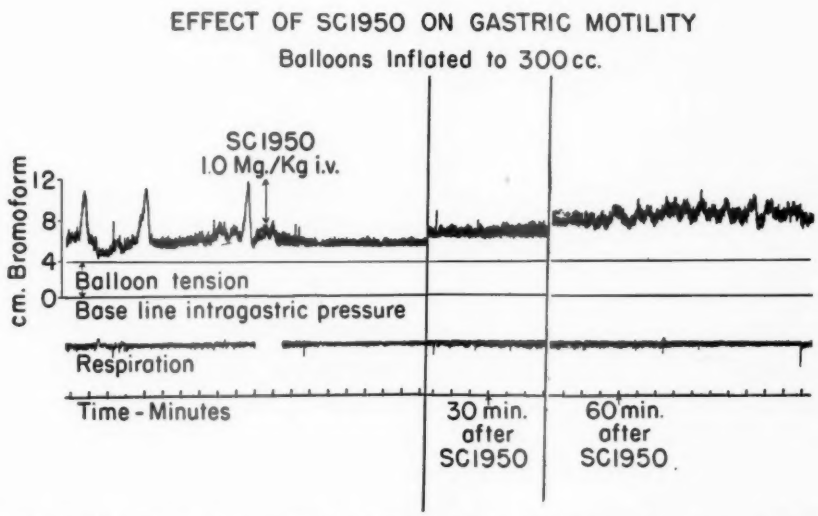

Fig. 2.—Gastrometric study demonstrating effect of SC 1950 on gastric tonus and contractile activity.

Intravenous administration of neostigmine, 0.5 mg., caused a return of gastric peristalsis in each of two patients tested following SC 1950, and intramuscular administration of 0.5 mg. caused return of contractions of the stomach or reversal of the gastric effects of SC 1950 in one of two patients. Urecholine, 2.5 to 5.0 mg. administered intramuscularly to four patients, also reversed the action of SC 1950 and caused an increase of gastric tonus and return of contractions.

As a control for radiographic studies of action of SC 1950 in patients, fluoroscopic and roentgenologic studies were performed after ingestion of barium on six patients with apparently normal gastrointestinal tracts. Gastric emptying was at least 50 per cent complete in one hour, averaging 70 per cent, and was 98 to 100 per cent complete in two hours in these patients. Gastric peristalsis and emptying were normal to fluoroscopic examination.

On another day these same studies were repeated, but SC 1950, 2.0 mg. per kilogram, was administered intramuscularly 30 minutes prior to barium. Immediately after ingestion of barium, fluoroscopic study showed no peristaltic activity or gastric emptying and average gastric emptying was 25 per cent at 1 hour, 40 per cent at 2 hours, and at 4 hours only two of the six had 100 per cent gastric emptying. In the control studies barium reached the cecum by 4 hours in all patients, but after SC 1950 it reached the cecum at 4 hours in only one of the six.

Four patients had continuous gastric aspiration through a Levine tube obtaining samples every 15 minutes over a 2 to 3 hour period. Intravenous administration of 1.0 to 1.5 mg. per kilogram of SC 1950 caused marked decrease in volume of gastric content aspirated and decrease in values for free and total acid in the specimens with corresponding change in pH. Free acid was present in all specimens prior to SC 1950 but was absent in two or more specimens in three of the four patients after SC 1950, and markedly reduced in the fourth patient.

C 7337.—The effect of C 7337 on the stomach was tested using 300 c.c. intragastric balloons in eight patients. C 7337, 1.0 to 1.5 mg. per kilogram, was administered intravenously. No consistent effect was seen. There was no appreciable change of gastric tone or of resting intragastric pressure. In five of the eight there seemed to be slight or insignificant decrease of activity for eight to twelve minutes following injection. Contraction waves following C 7337 in four patients were of greater amplitude than those before drug, but were less frequent in occurrence.

Roentgenographic and fluoroscopic studies of the gastrointestinal tract following ingestion of barium were performed in five patients who had no gastrointestinal complaints. Two received 75 mg. (1.2 mg. per kilogram) C 7337 orally 30 minutes before barium and three received 1.0 mg. per kilogram C 7337 intravenously 15 minutes before barium. Gastric peristaltic activity and emptying were normal as observed fluoroscopically. Roentgenograms at intervals following fluoroscopy revealed a slight delay of initial gastric emptying in two, there being only 10 and 25 per cent emptying in 1 hour, but complete emptying by 3 hours. Emptying rates of the others were within normal limits. Transit time through the small intestine was within normal limits in all five.

Continuous gastric aspiration with collection of samples at 15 minute intervals was performed in six patients. C 7337, 1.0 to 1.5 mg. per kilogram, was administered intravenously after basal secretion had been measured for 1 hour or more. Following the drug, five of the six had no significant change in milliequivalents of acid secreted during the 15 minute periods. The sixth had an

TABLE II. SC 1950 AND C 7337 IN MAN*

	SC 1950	C 7337
Administration	IV, IM (not oral)	IV, IM (oral)
Blood pressure	Reduced	Reduced
Cardiac rate	Slightly increased	Increased
Vascular reflexes: cold, breath holding	Blocked	Blocked
Temp. gradients extrem.	Blocked	Blocked
Gastrointestinal tone, peristaltic activity:		
Balloon studies	Reduced	Little change
X-ray studies	Reduced	No change
Gastric acidity	Reduced	No change
Side effects	Flushing, ptosis of lids, dryness of mucous membranes, loss of accommodation	Flushing, ptosis of lids, nasal congestion

*A comparison of route of administration and effects. Each drug was administered parenterally in comprarative studies.

increase of acid from an average of 0.47 meq. per 15 minute period over a 1½ hour period before C 7337 to 0.71 meq. per 15 minute period for a 1½ hour period after 1.0 mg. per kilogram. The pH of the specimens changed from an average of 2.2 before the drug to 1.8 afterward. The average secretion of acid during the 15 minute periods decreased from 1.21 meq. before C 7337 to 1.02 meq. in the five consecutive 15 minute periods immediately following drug in all six patients.

For convenience, mode of administration and effects of SC 1950 and of C 7337 have been summarized and compared in Table II.

C 7337 has been administered orally at intervals of 2 to 4 hours to thirty patients, who have continued the drug for periods of from 24 hours to 4 months. These have included nine patients with Raynaud's disease, three probably with Buerger's disease, one with arteriosclerotic occlusive disease, thirteen with hypertension, and three patients with atypical or causalgia-like pains in the extremities. Dose has varied from 25 mg. every 4 hours to 100 mg. every 2 hours. Since follow-up has not been carried out on most of these patients long enough for complete evaluation, statement of effect of treatment will not be given. Results indicate, however, that the drug is usually well tolerated, producing few side effects and not producing abnormalities evidenced by blood counts or urine analyses.

DISCUSSION

Results of the studies described here and summarized in Tables I and II indicate that two new drugs, one 2,6 dimethyl, diethyl piperidinium bromide (SC 1950), a ganglionic blocking agent, and the other 2 (N, p-tolyl-N (m′ hydroxyphenyl)-aminomethyl)-imidazoline hydrochloride (C 7337), an adrenolytic or sympatholytic agent, may be safely given to patients to produce effects which might be valuable in the treatment of certain diseases related to dysfunction of organs supplied by the autonomic nervous system. The first of these drugs, SC 1950, resembles in most of its actions the tetraethylammonium ion, or Etamon, blocking both sympathetic and parasympathetic divisions of the autonomic nervous system. The second drug, C 7337, resembles in its actions

Priscol and Dibenamine, blocking adrenergic pathways peripherally or at the end organ and therefore preventing the vasoconstricting or blood pressure elevating action of adrenalin and interrupting sympathetic nerve conduction without significant interference with the parasympathetic nerves. This drug is effective by oral administration.

CONCLUSION

Each of the two drugs described is apparently effective and well tolerated in patients.

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VENOUS PRESSURES IN THE SAPHENOUS SYSTEM IN NORMAL, VARICOSE, AND POSTPHLEBITIC EXTREMITIES

Alterations Following Femoral Vein Ligation

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ALTHOUGH in recent years much progress has been made in improving the operative attack on conditions resulting from venous stasis in the lower extremities, search is still being made for an operation which will insure normal venous return from the leg after this mechanism has been damaged by disease. Most procedures have consisted of the interruption, removal, or obliteration of incompetent or varicose veins in which the flow of blood is presumably reversed. Formerly these efforts were directed entirely at the saphenous system.[9, 13, 16, 17, 20, 22] Such an approach was found to be adequate only in patients whose saphenous veins alone were incompetent. In patients whose deep or communicating veins had been damaged by phlebitis[8] it was logical that attention was next directed to ligation of these veins in order to protect the skin and subcutaneous tissues against the noxious effects of increased pressures which were not normally relieved through the deep system.[11] More recently in such "postphlebitic" extremities direct attacks on the deep system itself have been made.[6, 10] Long-term clinical results in patients so treated are not yet available.

The proposal to ligate the deep veins of any given lower extremity in which venous stasis exists inevitably raises certain questions. Are all deep veins which have been damaged by a past phlebitis and which have become recanalized not only totally incompetent in returning blood from the limb but also harmful and best interrupted? Are all superficial veins which are dilated under such circumstances *ipso facto* likewise incompetent and in need of removal or obliteration, or are they compensatory in nature and accordingly useful? If we accept that femoral vein ligation is indicated in postphlebitic legs are the clinical tests of Trendelenburg and Perthes, which are designed to demonstrate incompetency of the deep system, so reliable that we can be sure of avoiding ligation of a normal femoral vein?

Answers to these questions and the evaluation of the various operative procedures have been difficult because available tests of venous function have depended upon visual or palpable estimates of venous distention which have been so rough as to have defied accurate numerical expression. The rate at which the veins of the leg fill below a tourniquet when the patient changes

Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 24-26, 1949.

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from a lying to a standing position (Trendelenburg) has been arbitrarily set at more than thirty seconds in order to indicate failure of reflux from the deep to the superficial system in the lower leg. Whether the limit of thirty seconds is proper or not, the estimation of the end point with fingers or eyes is approximate at best. The readiness with which the skin veins empty below a tourniquet when the patient is walking (Perthes), although in principle a better functional test, is also subject to similar criticism with regard to exactitude. In both these tests obesity or lack of prominence of veins may render impressions unreliable. A search for a more reliable test seems indicated.

Perthes[18] in 1895 first observed that the pressure in the veins of the leg decreased on ambulation and that this did not occur in extremities with incompetent veins unless these veins were occluded above the area observed. He made his observations by using a rubber band around the calf which he could watch contract as the pressure fell. Ochsner and Mahorner[17] stated that the pressure in varicose veins is greater than in normals. Rutledge[19] found this to be true of "secondary" varicose veins and Mayerson, Long, and Giles[14] observed it only in the reclining position. Other authors, however, found little difference in resting venous pressures between varicose and normal extremities regardless of the position assumed (Adams,[1] Beecher,[3] and Seiro[21]). Mayerson also found no difference in the standing position when the patient was at ease.

Those observers who have studied venous pressures in the lower extremity under conditions of exercise and straining, on the other hand, have found marked differences between normal and varicose extremities. Beecher, using an indirect method of determining venous pressures by means of a celloidin capsule sealed to the skin[2, 4] found the pressures in normals to fall to between 28 cm. and 75 cm. during ambulation and was able to describe the alterations at various stages during each step. In varicose extremities the pressure during walking persisted at 96 cm., this reading being the same as before walking. Seiro,[21] using the direct method of Moritz and von Tabora,[15] observed that the standing venous pressures varied with respiration, decreasing with inspiration and increasing with expiration. He also discovered that the pressure fell during walking in direct proportion to the competency of the saphenous valves, and that if the valves were incompetent occlusion of the saphenous vein above the needle caused as great a fall of venous pressure on ambulation as if the valves were competent. Veal and Hussey[23] performed similar tests on the popliteal vein and found marked rises in pressure during walking when there was obstruction of the deep system above due to thrombosis or pregnancy.

Delbet[7] found a great increase in pressure on straining when the pressure in the saphenous vein in the thigh was measured directly by means of a mercury manometer. Adams[1] using the direct method found that straining in patients with varicose veins caused venous pressures as high as 224 mm. of mercury and that that produced by straining after vein ligation in such a patient was 114 mm. of mercury, which was nearer the magnitude of pressure obtainable by straining in the normal.

These contributions suggest that the major circulatory defect in an extremity in which there exist incompetent veins is not a venous pressure which habitually reaches values higher than normal but a venous pressure which, like the normal, is, during resting, equal to the height of the column of blood between the heart and the area tested, but which, unlike the normal, fails to fall on muscular exercise. It also appears that the magnitude of pressures obtained on straining in patients with varicose veins is greater than in the normal.

The present study was made to discover whether determinations of venous pressure in the saphenous vein in the erect position, both resting and walking, as performed by Beecher and Seiro might serve as a more accurate Perthes test for venous function in the lower extremity. It was stimulated by the hope that the answers to some of the questions posed might be made clear.

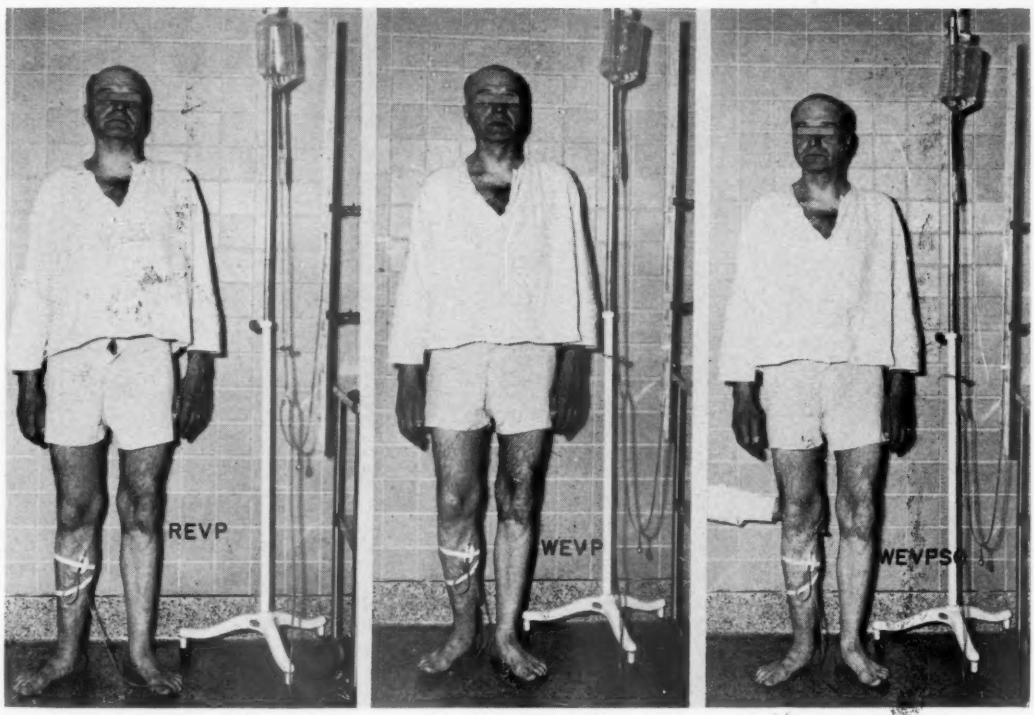

Fig. 1.—The venous pressure apparatus is shown in use with the patient standing still (REVP), with him walking (WEVP), and with him walking in the presence of saphenous vein occlusion (WEVPSO).

METHODS USED

The method used was that of Moritz and von Tabora (Fig. 1). A venepuncture is performed in one of the saphenous veins of the calf or one of their tributaries with a No. 20 gauge needle. This is connected by a rubber tube six feet in length to an elevated reservoir of physiologic salt solution which is allowed to drip continually into the vein except during the time that the pressure readings are being made. A side arm in the middle of this tube leads to a manometer which consists of a glass tube 60 cm. in length with a bore of 3 mm. fastened to a vertical centimeter rule. The manometer is filled with solution

from the reservoir, and the venous pressure reading is made by eliminating the reservoir from the system and allowing the fluid in the manometer to seek a level.

All readings were made in the erect position. The resting erect venous pressure was considered to be normal if the manometer level fell between the projection of the right auricle, arbitrarily set at the space between the fourth and fifth costal cartilages, and 15 cm. above it. In testing any individual extremity this point was then taken as 0, and all changes from it were expressed in centimeters of water as fall or rise.

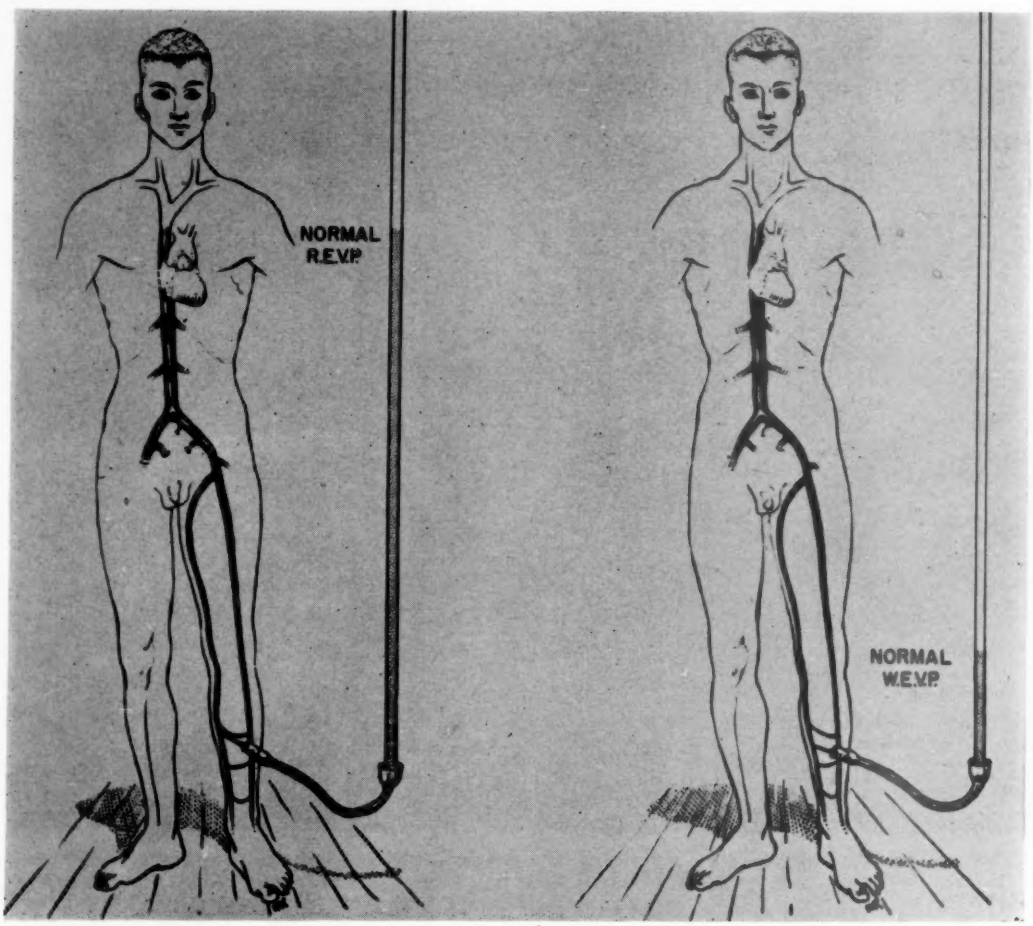

Fig. 2.—A diagrammatic illustration of the differences in venous pressure in the saphenous system of the normal lower extremity between the resting and ambulatory states.

Three pressures were ordinarily determined, the resting erect venous pressure (REVP), the walking erect venous pressure (WEVP), in which the patient walked in place at 120 steps a minute, and the walking erect venous pressure during saphenous vein occlusion (WEVPSO) (Fig. 2). Occlusion of the saphenous vein was always performed with the palpating finger. The value given is the greatest fall obtained as determined by testing occlusion at various points usually in the following order: the internal saphenous vein at the

femoral condyle, the external saphenous vein below the popliteal space, other points where communicating veins may seem clinically to be incompetent.*

The apparent difficulty of making comparisons between individuals of different heights, who normally would have different degrees of pressure fall during ambulation, were found after numerous calculations to be insignificant with respect to the purpose of the test. Fig. 3 is a graph in which the fall of pressure in centimeters was plotted against the fall expressed in the percentage of the distance from the base line (the heart) and the floor. It is apparent that the factor of height in comparing two individuals of different heights would never lead to an error of greater than 10 cm. and then only when the fall was maximal. It was, therefore, considered wise to persist in the more convenient method of expressing pressures, namely, centimeters of fall as read on the manometer.

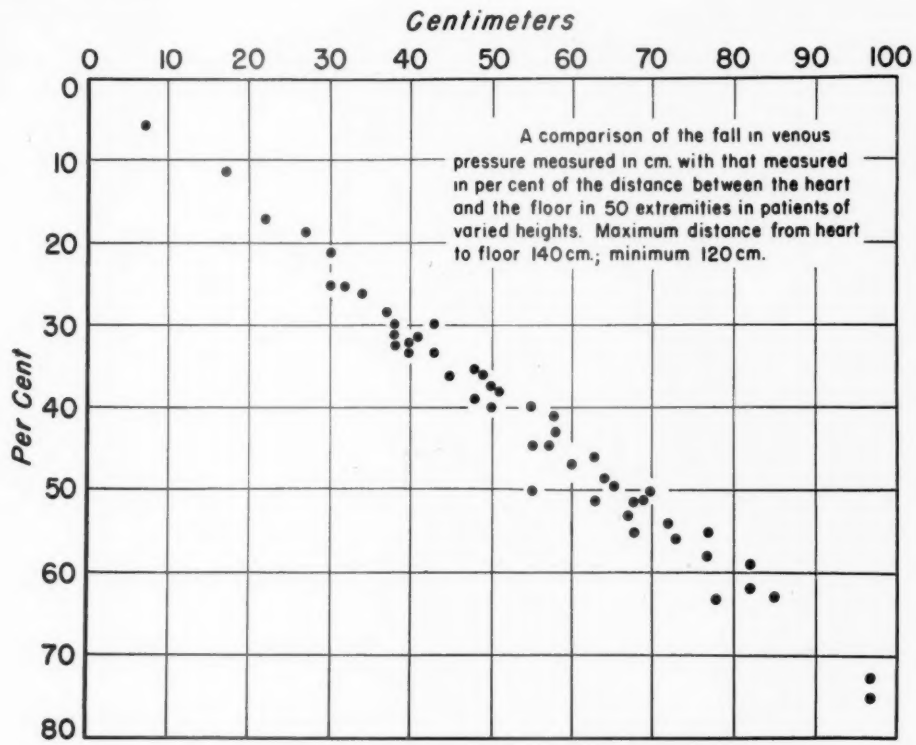
Centimeters
0 10 20 30 40 50 60 70 80 90 100
0
10
20
30
40
50
60
70
80
Per Cent
A comparison of the fall in venous pressure measured in cm. with that measured in per cent of the distance between the heart and the floor in 50 extremities in patients of varied heights. Maximum distance from heart to floor 140 cm.; minimum 120 cm.

Fig. 3.

The extremities tested fell in three clinical groups: normals, those having uncomplicated varicose veins, and those which showed postphlebitic stasis. The normal extremities were those causing no symptoms and possessing no prominent varicosities, although prominent straight veins did not exclude an asymptomatic extremity from the normal group. The varicose extremities were those which were symptomatic with large or small varices plus those with small varices which were asymptomatic. Often the dividing line between a normal and a varicose extremity was hard to draw. The postphlebitic extremi-

*Dr. E. J. Harris and Dr. J. M. Carey of the resident staff of the West Roxbury Veterans Hospital and Drs. J. E. Thompson, P. T. Brooks, and G. V. Rodkey of the resident staff of the Massachusetts General Hospital gave valuable additional help in performing the tests.

ties were those with a past history of phlebitis and current venous stasis. In these the Trendelenburg test and the Perthes test tended to indicate poor function of the deep system; in many, phlebograms were done which showed failure of filling or lack of valves in the system; and in most the femoral vein was biopsied at operation and shown to have been damaged by past inflammation.

In order to determine whether it is always important to use the same vein on repeat tests in the same extremity, a group of observations were made with two simultaneous recordings in different veins in the same extremity. Observations were made in 3 normal extremities. If D equals the vertical distance between the two needles and F is the difference in WEVP in the two manometers, the ratio D/F should be a constant one in different subjects in order to enable us to make a calculation to correct for a different level of the needle on repeat tests in any case. In our 3 patients the ratio D/F was 34/14, 32/32 and 45/15. In other words, although the fluid level in the manometer attached to the lower needle fell to a point which was nearer the floor than that in the higher needle, it did not always do so in predictable amounts. Simultaneous tests were also made at two different points in 14 varicose or postphlebitic extremities. Here also the additional fall in pressure found in the lower vein was noted but was unpredictable in amount. Therefore, we have concluded that the same vein must be used on all repeat tests in the same patient.

RESULTS

Resting Erect Venous Pressure (REVP).—The REVP was determined in 102 extremities. In 13 of these the veins were normal, in 77 varicose, and in 12 postphlebitic. In all but 2 of these extremities the fluid level came to rest between 1 cm. and 15 cm. above the fourth and fifth right costal cartilage. In 1 of these patients a stable level of pressure could not be found while testing the normal leg because the patient was nervous, could not stand still, and had a marked postural sway. In the other of the 2 exceptions we were concerned with a patient with varicose veins who had asthma and whose recumbent venous pressure was 28 cm. above the level of the right auricle. The REVP in his case was 20 cm. above the fourth right costal cartilage.

Walking Erect Venous Pressure (WEVP).—The WEVP was determined in 13 normal, 77 varicose, and 12 postphlebitic extremities. Fig. 4 demonstrates a comparison between the results in these three groups in terms of maximum, minimum, and average change.

Normal extremities: There was an average change in normal extremities of –51.7 cm. with extremes of –28 cm. and –72 cm. The standard deviation was 13.5 cm. and the standard error of the average ±3.8 cm.

Varicose extremities: The average change of pressure in the varicose extremities was –26.6 cm. with extremes of –3 cm. and –82 cm. The standard deviation was 16.9 cm. and the standard error of the average ±2.4 cm.

Postphlebitic extremities: The average change in pressure in postphlebitic extremities was –1.8 cm. A maximum fall of –10 cm. and a rise of +16 cm. were

the extremes. The standard deviation was 8.5 cm. and the standard error of the average ±2.4 cm.

Walking Erect Venous Pressure During Saphenous Occlusion (WEVPSO).—The WEVPSO test was performed in 10 normal, 74 varicose, and 12 postphlebitic extremities.

Normal extremities: The average change of pressure during the test in normal extremities was –45.2 cm. with a maximum of –72 cm. and a minimum of –25 cm. The standard deviation was 12.7 cm. and the standard error of the average ±4.0 cm. In 6 extremities the occlusion of the saphenous vein caused no change in pressure from the WEVP without occlusion. In 2 there was a further fall on occlusion; in 2 there was a rise above the WEVP level.

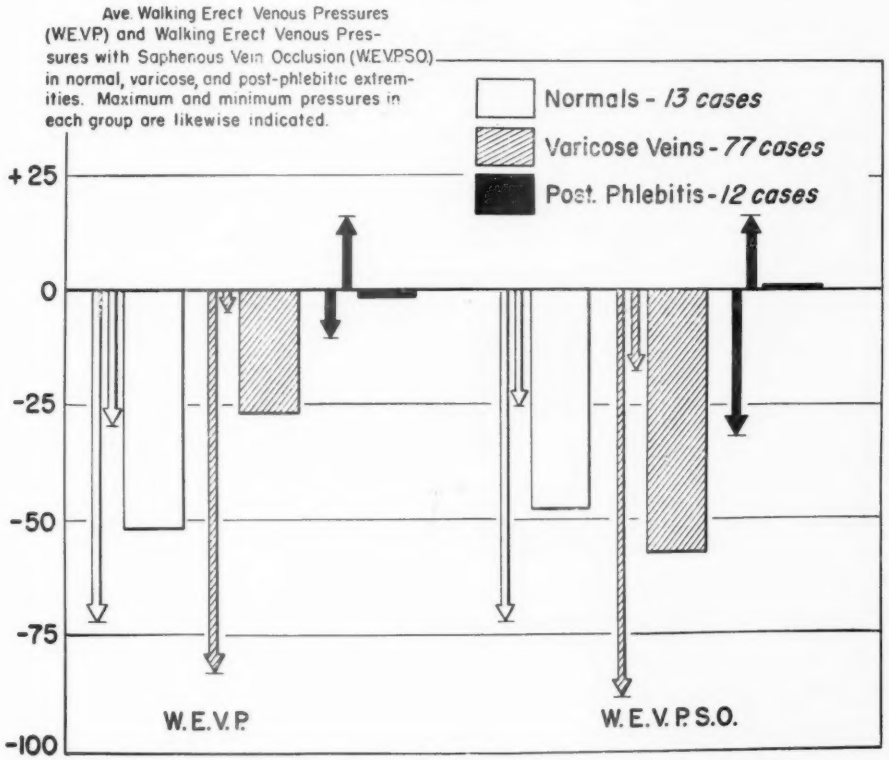
Ave. Walking Erect Venous Pressures (WEVP) and Walking Erect Venous Pressures with Saphenous Vein Occlusion (WEVPSO) in normal, varicose, and post-phlebitic extremities. Maximum and minimum pressures in each group are likewise indicated.
Normals - 13 cases
Varicose Veins - 77 cases
Post. Phlebitis - 12 cases
+25
0
-25
-50
-75
-100
W.E.V.P.
W.E.V.P.S.O.

Fig. 4.

Varicose extremities: An average fall of –57.2 cm. took place in the varicose extremities with extremes of –18 cm. and –88 cm. The standard deviation was 14.3 cm. and the standard error of the average ±1.7 cm. In each patient this reading was lower than in the same test in that patient taken during walking without saphenous occlusion.

Postphlebitic extremities: During the test in postphlebitic extremities the average change in pressure was a rise of +0.66 cm. The standard deviation was 13.5 cm. and the standard error of the average was ±3.8 cm. In only 1 patient of this group did this test show a lower fall than in the same test without saphenous occlusion. This occurred in a patient whose WEVP was –3 cm. but whose WEVPSO was –30 cm. In spite of a definite history of milk leg, how-

ever, the superficial femoral vein showed at operation only minimal evidence of past inflammation and may have been normal. In 1 of the other 11 extremities there was no further change in pressure when the saphenous vein was occluded. In the remaining 10 extremities saphenous occlusion resulted in a venous pressure in the saphenous vein which was 1 cm. to 10 cm. higher than that without occlusion.

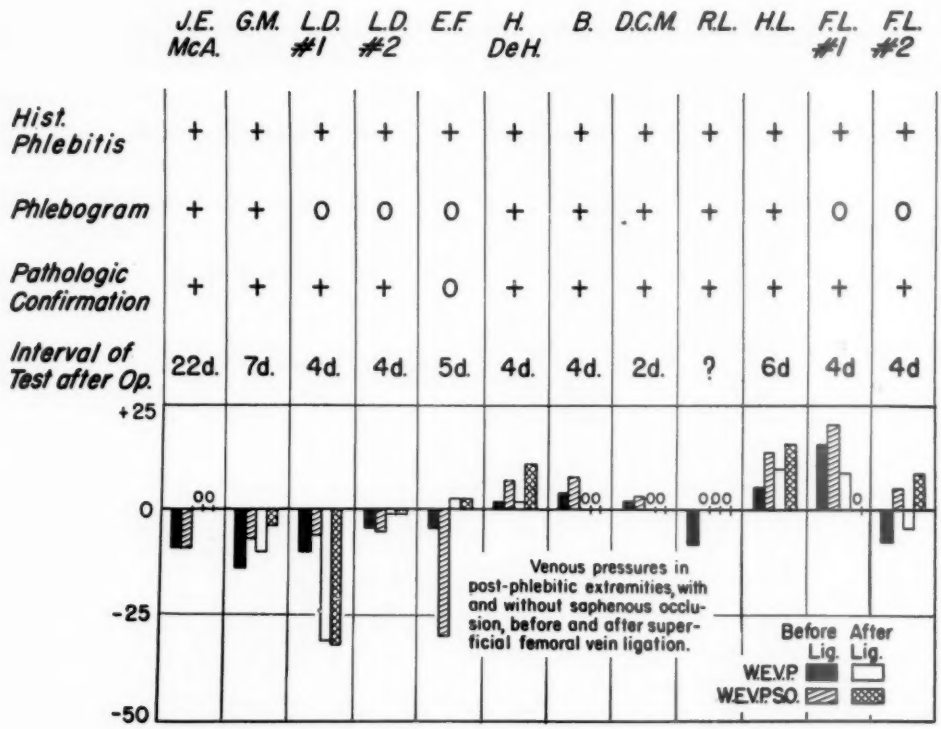

Fig. 5.

Influence of Femoral Vein Ligation on Postphlebitic Stasis.—In 12 postphlebitic extremities pressure determinations were made after superficial femoral vein ligations. These were compared with those made before ligation in the same patients. They were all done within one month after the procedure, most of them within the first week postoperatively. Fig. 5 shows the variations in the WEVP with and without saphenous occlusion between the pre-and postoperative states. In 5 of the extremities the WEVP was higher in the postoperative state than in the preoperative. This increase in pressure on walking was not great, the maximum being 7 cm. In 3 extremities there was no change in WEVP after ligation and in 4 there was a fall. In all but 1 of the instances in which a fall occurred it was insignificant in degree (20 cm. more than before operation). If the saphenous vein was occluded during walking in the postligation extremity there was no pressure recorded which was lower than the pressure prior to occlusion in any case. In 7 extremities there was no change in pressure, and in 5 there was a further rise.

Comment.—A quantitative expression of the differences in the function of the venous systems in the lower extremities of patients with normal, varicose,

or postphlebitic venous circulations, as shown in terms of average figures in Fig. 4, reveals that the patient with a normal extremity can, on the average, lower the pressure in the saphenous vein by walking by the vertical distance between the heart level and the level of the upper thigh. The extremity with uncomplicated varicose veins can, on the average, do only about half this well, whereas the postphlebitic extremity can lower it essentially not at all. Occlusion of the saphenous vein does not greatly alter the pressures in the normal or the postphlebitic leg but will drop the pressure in uncomplicated saphenous varices to a level which in our group was even lower than the normal.

The tests have revealed that clinical judgment in placing the extremities in the 3 groups was occasionally faulty since, as is shown in Fig. 4, each group has some extremities in it which, according to venous pressure reactions, do not belong there. The extremes of fall on WEVP in normal extremities were 28 cm. and 72 cm. In varicose extremities they were 3 cm. and 82 cm., respectively. It seems obvious from these tests that the patient in whom the pressure fell 82 cm. on walking without occlusion had good venous function even though the veins were prominent and showed a few small varices. On the other hand in the patient with the normal extremity whose WEVP was only –28 cm. and showed a WEVPSO of –45 cm., one could postulate that although no varices were seen, the saphenous vein is already incompetent and frank varices may develop in the future.

The same difficulty may be encountered in making the diagnosis clinically between a varicose extremity and one which has had phlebitis. On this point the chief value of the test lies in the fact that the average WEVPSO in the varicose extremity was –57.2 cm., whereas there was no fall in the postphlebitic group.

With regard to the early postoperative results following femoral vein ligation for postphlebitic stasis these tests have, in most cases, shown little improvement in venous function. It is to be emphasized, however, that these observations were made in the early postoperative period and that any beneficial effect which femoral vein ligation may have could conceivably not be manifest for several months or until the collateral circulation through subcutaneous and muscular veins has had time to develop. Studies of this are being made at present.

Only partial and preliminary answers can be given to the questions posed earlier in the paper. The studies on postphlebitic extremities before and after operation suggest that deep veins which have previously been damaged by disease are incompetent but that ligation of them does not give dramatic improvement in venous function. They also suggest that in many postphlebitic extremities the saphenous veins, although prominent and slightly varicose, may perform a useful, though incomplete, function. The answer to the third question, as to whether this test can give better information with regard to the function of the deep system than tests dependent on visual or tactile estimations of venous filling, has, in our opinion, been given in the affirmative. All extremities operated upon which have shown faulty function in the deep veins according to these tests have demonstrated abnormal femoral veins at operation.

There are two points with regard to the technique of the test which, although not apparent in the figures, seemed significant while the tests were being made. First, the rapidity of pressure changes which took place during ambulation varied widely in different extremities. The responses in the postphlebitic extremities were notoriously slow and sluggish, those in normal and in varicose extremities after saphenous occlusion were rapid and definite. Responses also tended to vary in speed in the same extremity in inverse proportion to the length of time the patient had been in the erect position prior to the test. Second, a difference between two readings of a few centimeters must be considered without great significance unless it is repeatable. Factors introduced by involuntary straining and by failure to stand erect combined to make us feel that it is better to interpret changes as significant in terms of five or tens of centimeters rather than of single centimeters. The standard deviations of between 8.5 and 16.9 cm. in the data which make up Fig. 4 are expressions of this.

It must also be remembered that the direct method of determining pressures does not detect the rapid changes which have been shown by Beecher to take place during a single step. The levels here observed must be considered to represent averages maintained for several steps. This may, however, be advantageous in estimating the over-all effect of the venous return.

The measurement of venous pressure in the saphenous system of veins of the lower extremity during walking does not introduce a new concept into the understanding of venous stasis in the leg. It does, however, re-emphasize the importance of the circulatory defect in this condition as has been previously done by Perthes, by Beecher, by Seiro, and by Adams. We have attempted to adapt their work to problems as we see them in the clinic. The method, which is simple in conception, but occasionally cumbersome in execution due to difficulty in keeping the recording needle securely in a vein, is not to be recommended for the routine testing of all clinical cases of varicose veins. It is more adapted to the study of limbs in which the presence or absence of incompetency of the deep system is in doubt. In these patients a more accurate Perthes test can thus be done and by it the results of therapy can be checked.

SUMMARY

1. A method, originally described by Beecher and by Seiro, for the evaluation of venous stasis in the lower extremity was used to test 102 extremities. It consists of measuring the venous pressure in the saphenous system while the patient is in the erect position and comparing the values found on standing still with those on walking with and without digital occlusion of the saphenous veins.

2. The average fall of pressure on walking without saphenous occlusion was 52 cm. in normal extremities, 27 cm. in varicose extremities, and 2 cm. in postphlebitic extremities. In varicose extremities occlusion of the saphenous vein during walking increased the fall in pressure to normal values (–57 cm.), whereas in normal and postphlebitic extremities the pressure fell slightly less well on walking with occlusion of the saphenous vein than without it.

3. Measurements of venous function in this manner before superficial femoral vein ligation for postphlebitic stasis and again in the early postoperative period failed to demonstrate consistent improvement after the procedure.

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AN IMPEDANCE GAUGING SYSTEM FOR MEASUREMENT OF BIOLOGIC PRESSURE VARIABLES

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PROJECTED cardiovascular and cardiopulmonary studies at the University of Kansas Medical Center made necessary the development of a new gauging system for the measurement of biologic pressure variables. This work is to be carried out on laboratory animals as well as on patients in different geographic areas of the Center. The problem was further complicated by our desire to study animals and patients during operations within the major body cavities. A fixed optical system thus seemed impractical. Piezometers are generally used in industry, however, until recently only a few have been employed in biologic studies. Best known of these devices is the unbonded resistance wire strain gauge. Use of this type of instrument was abandoned because of technical difficulties in construction and questionably adequate frequency response. Capacitance gauges have the advantage of high frequency response and simplicity in construction, however, they are unstable due to lead motion causing varying shunt capacity. Piezo-electric crystals are unsatisfactory for this application since they fail to indicate static pressure. Because of high output and high frequency response, the displacement sensitive vacuum tube is well suited for biologic pressure measurements. We have not had an opportunity to evaluate this method. An impedance gauging system has these advantages: desirable physical characteristics, relative simplicity in construction and operation, and adequate sensitivity and frequency response. The system which is to be described is the result of a cooperative venture by our electronics laboratory and an instrument company* and the gauge is now being manufactured by the latter organization.

The gauge consists of two coils surrounding an axially placed iron slug (Fig. 1). These two coils make up adjacent arms of an impedance bridge. The other two arms of the bridge are represented by a center tapped adjustable resistor. A third coil excited by a 5,000 cycle carrier is situated between the pickup coils. The iron armature is fastened to the center of the gauge diaphragm. At zero pressure the bridge is balanced for zero signal output. The output is then taken from the outer terminals of the paired pickup coils and is fed through a transformer to the first grid of the channel amplifier (Fig. 2). As pressure is applied to the diaphragm the armature moves in relation to the coils unbalancing the bridge and causing a signal to appear at the amplifier input. The magnitude of the signal is directly proportional to the applied pressure. This signal appears as an increasing or decreasing level of the 5,000 cycle carrier. After suitable amplification, the carrier is demodulated leaving only the pressure-wave envelope. This voltage is then applied to a galvanometer in the recording oscillograph. A cathode ray tube with long persistence screen

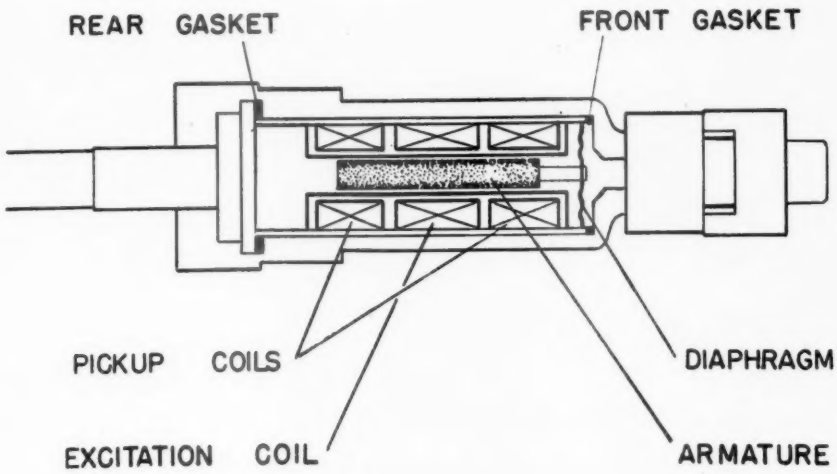
Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 24-26, 1949.

This work was made possible by a grant from the Emergency Commission of the State of Kansas.

*The Hathaway Instrument Company of Denver, Colo.

is used for monitoring this pressure wave. To obtain the relatively high voltage required to excite this tube an additional amplifier and demodulator are employed. For adequate comparison of several successive pulse waves a low frequency sweep oscillator is used. It may be adjusted to sweep as slow as .2 cycle

Fig. 1.



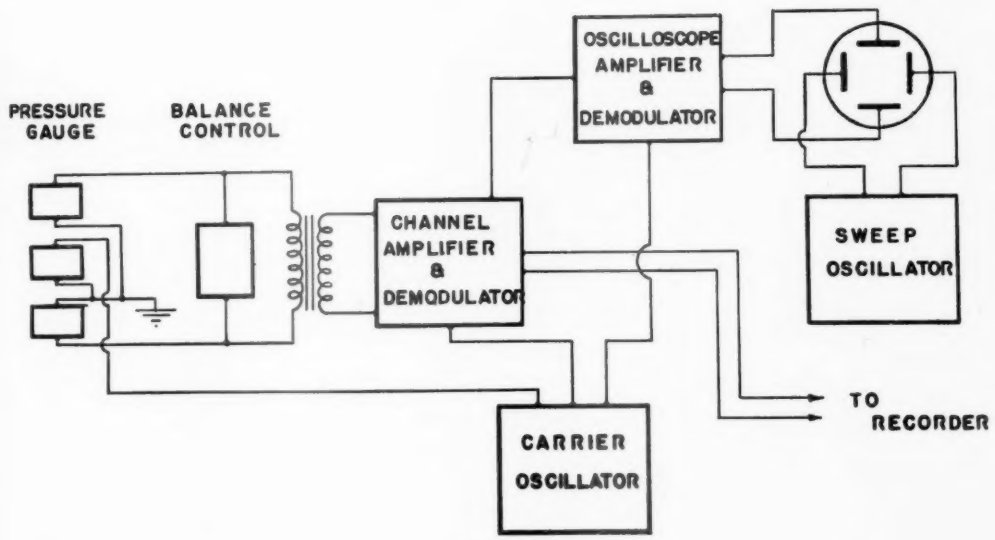


Fig. 2.

Fig. 1.—Schematic drawing of the pressure-sensing element.
Fig. 2.—Block diagram of the gauging system.

per second, thus permitting visualization of pulse waves during any five second period. Our present instrument is capable of synchronously recording five pressure variables. The gauge may be calibrated against a mercury manometer for a standard deflection on the record and on the cathode ray tube. After this adjustment has been made, a switch permits attenuation of the deflection sensitivity in the following proportions: 0-400, 0-200, 0-100, 0-50, and 0-25. To attain perfect balance a variable resistor and capacitor are regulated from the

instrument panel. Inductive balance is obtained in the gauge itself. An output balancing control is also available on the instrument panel, this allowing precise composition of the oscillograph record.

The pressure-sensing element is housed in a steel cylinder, to the front of which the gauge diaphragm is sealed (Fig. 3). Leads emerge from the opposite

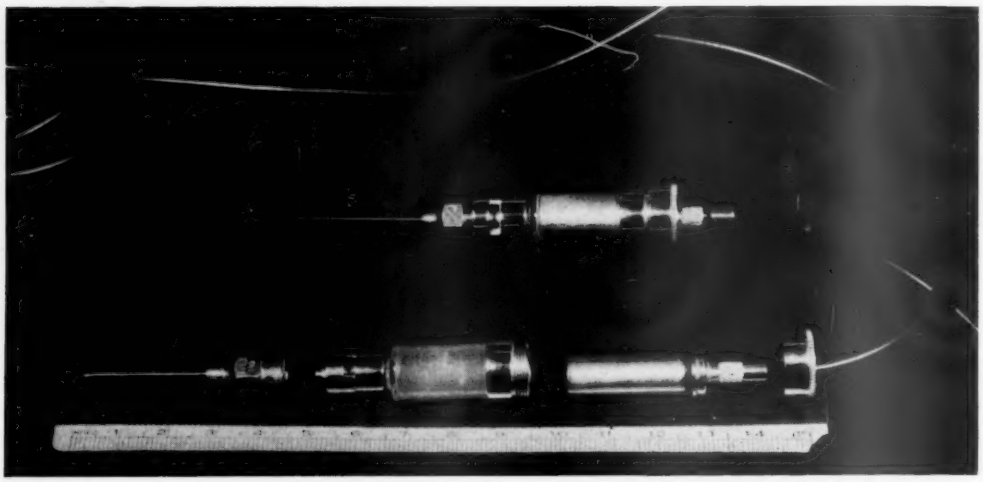


Fig. 3.—PS-8A impedance gauge shown assembled above and below, from left to right, a standard needle, the glass shell with adaptor, the steel cylinder containing the pressure-sensing element, and the lead connector together with its threaded collar.

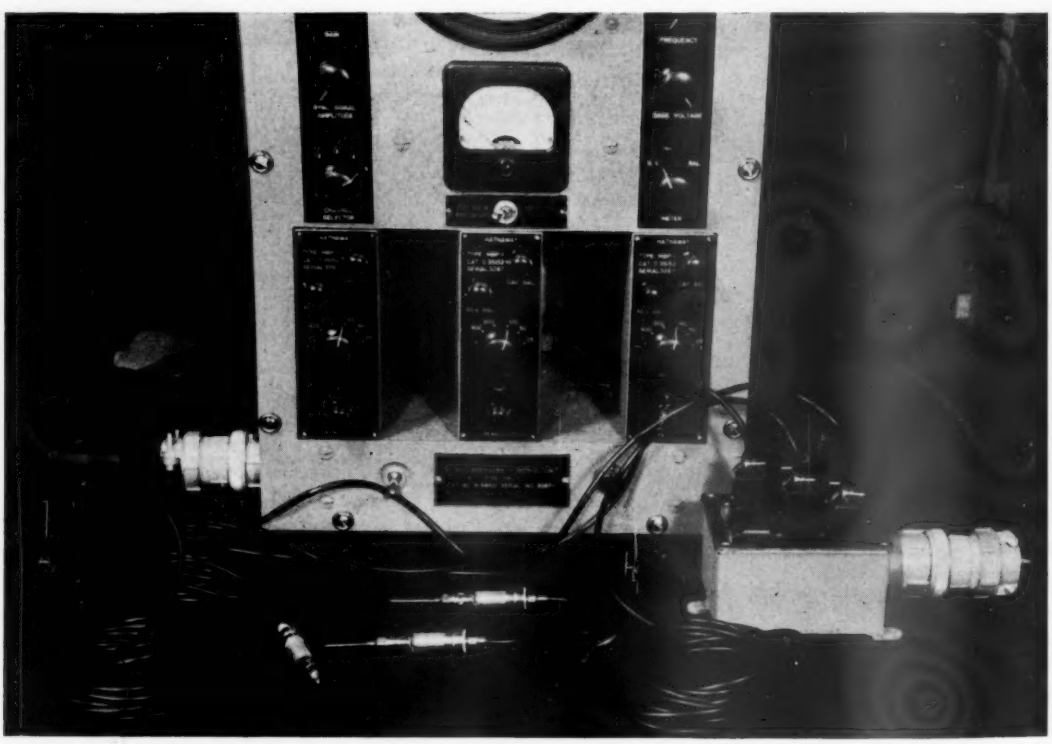


Fig. 4.—Three assembled gauges shown plugged into the junction box at right which is in turn connected to the controller unit in the lower part of which three channel amplifiers are seen.

Fig. 5.

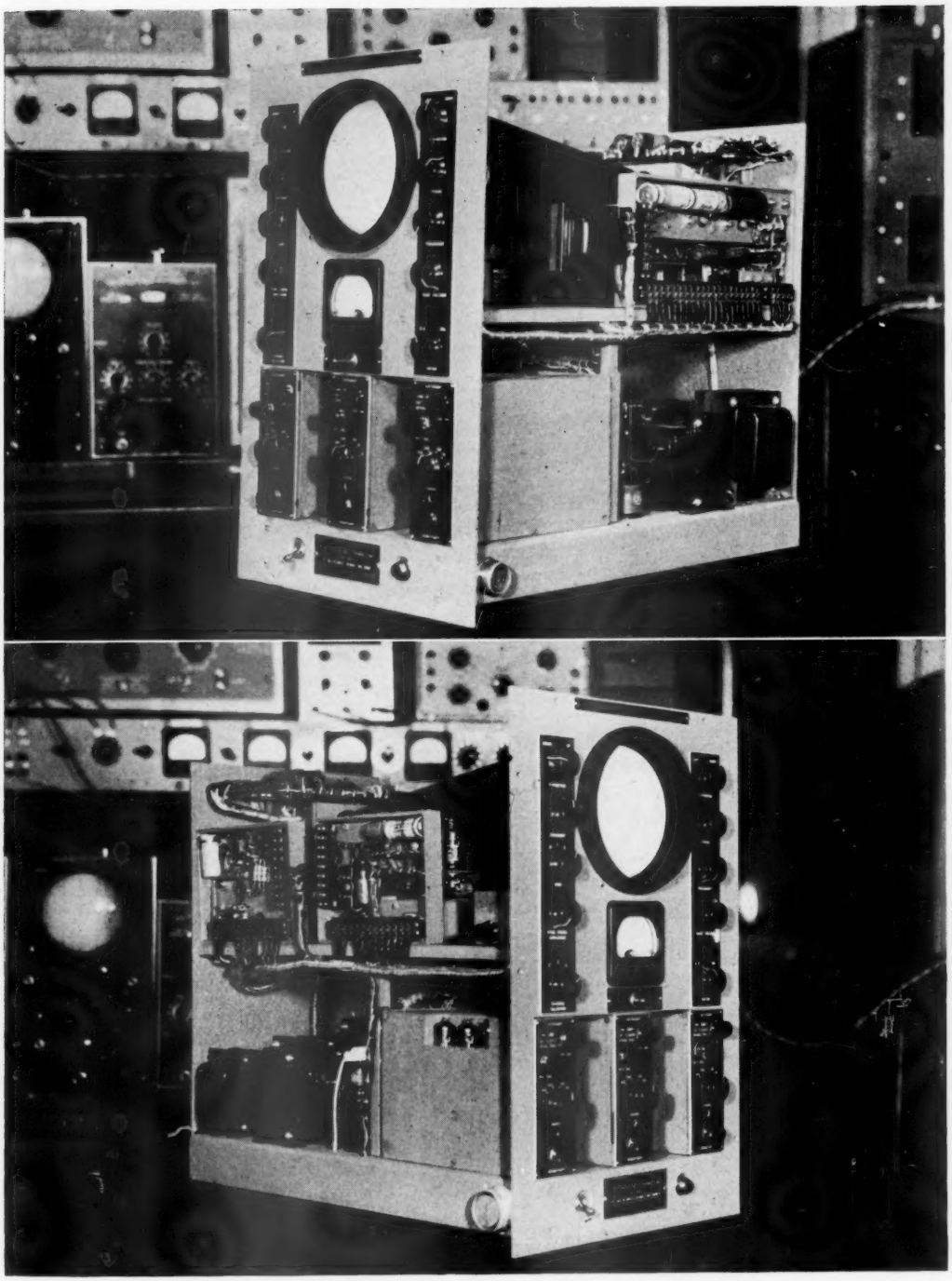


Fig. 6.

Fig. 5.—The MBC-1 controller with case removed showing the common carrier oscillator in the rear of the upper level together with the cathode ray tube and its controls. Three channel amplifiers are shown in position below.

Fig. 6.—View of left side of controller unit showing the amplifier and sweep oscillator for the cathode ray tube above.
fiers are seen.

end of the cylinder, which is also sealed. The cylinder snugly fits a shortened 2 c.c. glass Luer syringe, the residual chamber being isolated to the diaphragm face by means of a front and rear gasket. The cylinder is held firmly against these gaskets by means of a threaded collar. The light flexible gauge lead is fifteen feet long and is fitted with a four-terminal plug. This entire unit has been designed to withstand either hot or cold sterilization routines.

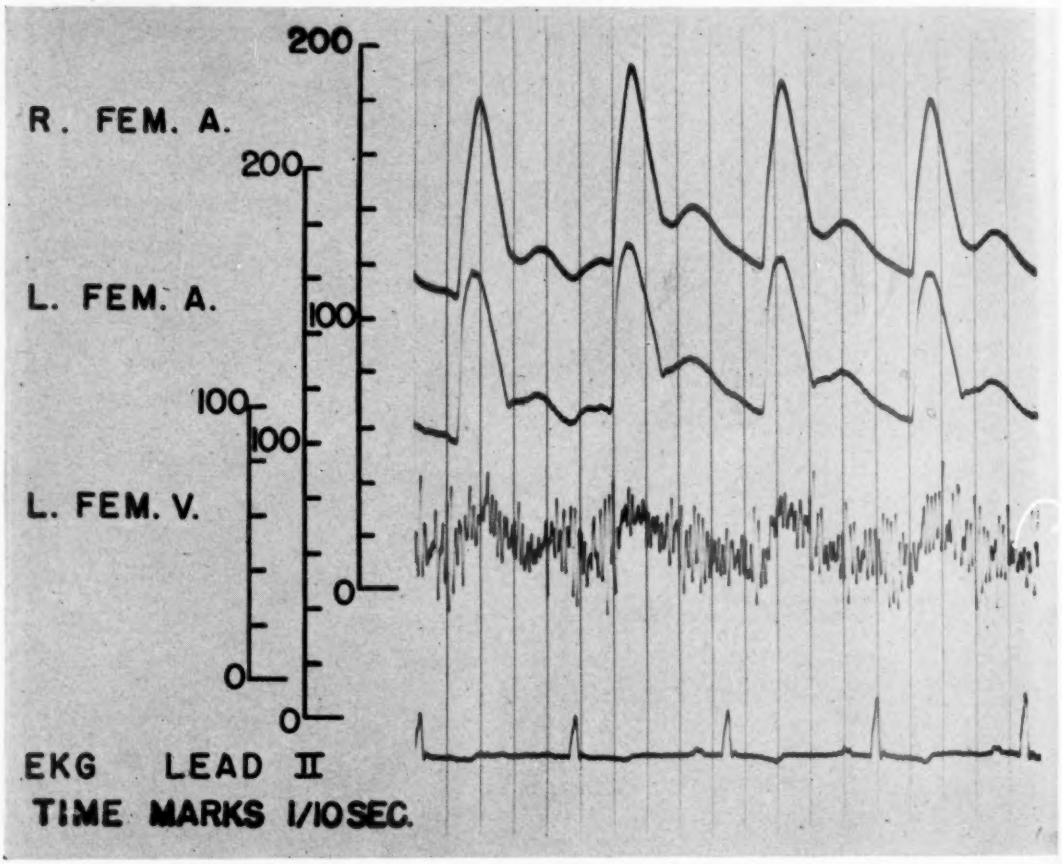


Fig. 7.—Oscillograph record of blood pressures in a dog with an experimental fistula between the left femoral vein and artery. In the vein at the site of the fistula high-amplitude, high-frequency wave forms in the audible range of 100 cycles per second are seen. Low-amplitude, rapid pressure transients are observed in the artery proximal to the fistula. The contralateral femoral artery pulse is unaffected and the electrocardiograph is normal. Both systolic and diastolic pressures are lower in the artery on the side of the fistula than on the opposite normal side.

All five gauges may be plugged into a junction box, which in turn is connected to the control unit containing the five channel amplifiers, the common carrier oscillator, and the cathode ray tube together with its controls, amplifier, and sweep oscillator (Figs. 4, 5, and 6). Each amplifier may simply be pulled out of the controller to be replaced by one with similar characteristics or one of different design such as might be employed in electrocardiography. A multichannel cable with appropriate fittings connects the controller to the recording oscillograph. In our particular installation the controller and oscillograph are situated in a special laboratory together with other instruments. Various working areas in the hospital are connected to the laboratory by means of a multichannel coaxial cable of 600 feet maximum length.

Static response of this system has been found linear over the range of 0-400 mm. of mercury (Fig. 8). The natural frequency of the fluid-filled gauge is in excess of 600 cycles per second. When fitted with a 20 gauge needle, one and one-quarter inches long, the frequency response is flat to 100 cycles per second

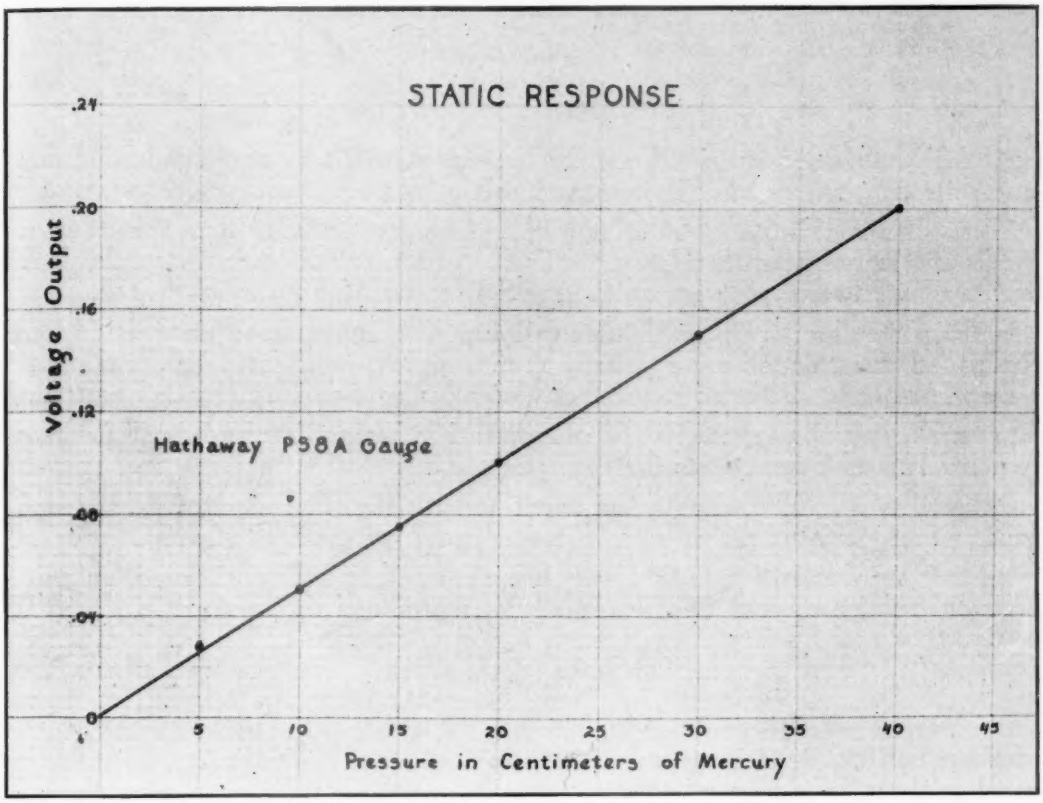


Fig. 8.—Static response of the PS-8A impedance gauge.

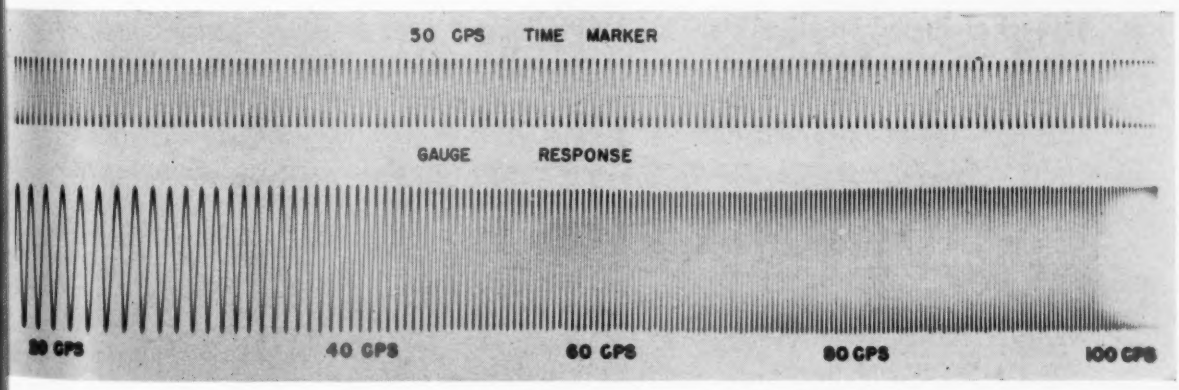


Fig. 9.—Frequency response of the PS-8A impedance gauge.

(Fig. 9). A phase lag of about 30 degrees appears at 100 cycles per second. This phase distortion will not be apparent on any records likely to be made in connection with biologic investigations.

The writers wish to express their appreciation for the interest and cooperation of Mr. C. M. Hathaway and Mr. Warren Tilton of the Hathaway Instrument Co., Prof. H. C. Roberts of the University of Illinois, and Mr. Oliver Boutrous.

FACTORS AFFECTING THE DIAMETER OF LARGE ARTERIES WITH PARTICULAR REFERENCE TO TRAUMATIC SPASM

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SIGNIFICANCE OF THE PROBLEM

SPASM of large arteries has long been recognized as a clinical condition following trauma in the neighborhood of the vessels or directly to them, and it has been called by many names such as traumatic arterial spasm, myogenic spasm, or "arterial stupor."

Traumatic spasm is a well-known complication of fractures, particularly at the elbow joint, where Volkmann's ischemic contracture may be an end result. Dissection of a large artery, such as the femoral during the operation of femoral vein ligation or for purposes of arteriography, may produce spasm as may the injudicious application of a tourniquet or a near miss by a projectile such as a rifle bullet.[1-5]

Opinion is divided as to the exact mechanism of production of the condition and particularly as to the role played by nervous components. No really efficacious form of treatment has been yet devised and this is not surprising when the scant knowledge of the physiology of large arteries is considered.

PREVIOUS WORK

The clinical side of the problem has been considered at length by many authors. Reports of large artery spasm following the near passage of fast projectiles were numerous during World War I when the condition was sometimes referred to as Kroh's arterial stupor. More recently other authors, Cohen,[6] DeBakey and Simeone,[7] and Griffiths[8] have been interested in the subject and good bibliographies have been compiled.

Fundamental experimental work on the physiology of large vessels has been more scant than clinical observations. Lister[9] performed some experiments on the arteries of a horse at a time when he was interested in the effect of posture on the blood supply of the limbs and in the means of producing a bloodless operating field. He used calipers and could detect no difference between the diameter of large arteries at systolic and diastolic pressure as they pulsated and therefore concluded that alterations in blood pressure did not affect the width of arteries. This is a conclusion with which our experimental findings are at variance.

MacWilliam[10] of Aberdeen in 1902 published the results of experiments on large arteries excised from oxen. Mechanical trauma was found to produce spasm but electrical stimulation in various forms had no effect except

This work was supported in part by a grant from the Life Insurance Medical Research Fund.

Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 24-26, 1949.

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for very strong galvanic currents which were found to cause contraction. Many of his investigations such as the effects of extreme heat and cold and the application of various chemicals, however, bore little resemblance to physiologic or therapeutic measures, besides carrying the disadvantage of being in vitro experiments. Grant[11] recorded the effects of various stimuli upon the arteries of the rabbit's ear observed through a microscope, and although these vessels are considerably smaller, they often behaved in a similar way to the larger arteries, such as the femoral, observed in this study.

More recently, attention has been focused upon the question of nervous reflexes causing large artery spasm (Barnes, Trueta, and others[12, 13]). These workers investigated the role of vascular factors in the crush syndrome by applying tourniquets to the limbs of rabbits and visualizing the arterial tree by means of radiopaque injections. They were able to demonstrate a shrinkage of the arterial tree in the leg contralateral to the tourniquet and concluded that this was due to a nervous reflex.

Both local and reflex spasm have been investigated in the experiments which will be described here.

METHODS

The techniques used in the present study will be outlined before the experimental results are recounted. Rabbits and cats were used. Endotracheal cannulation, bilateral vagotomy, and division of the cervical sympathetic were performed as a routine.

Measurement of the Arterial Diameter.—Most observations were made upon the femoral artery of rabbits or cats, just below the inguinal ligament. The artery was exposed by making a short transverse incision through the skin and deep fascia, and by careful dissection with a sharp scalpel defining its borders for about one-quarter inch in extent. A thin layer of voluntary muscle overlies the femoral artery in the rabbit and this had to be removed. Care was taken to leave as much connective tissue as possible around the artery in each case so that any possible periarterial nerve plexus in the adventitia was left intact.

In those cases in which the effect of mechanical trauma was being studied, the dissection was carried beneath the artery as well so that a length of cotton thread could be passed under it and used to give the artery a sharp stretch.

In certain cases where it was desired to exclude nervous factors, the adventitia was removed during the dissection which was carried up and down the artery for a somewhat greater length. This, for example, was the routine method of dissection in those cases where reflex spasm was being studied and for which sympathectomy had been performed to exclude nervous mechanisms.

In order to avoid drying of the arterial or surrounding tissues they were kept covered by a shallow pool of liquid paraffin. Visualization through this was good and the lateral edges of the artery were well defined.

When the effects of agents such as electrical stimulation or mechanical trauma applied directly to the arterial wall were being studied, the liquid

paraffin could not be used and, instead, the tissues were kept moistened from time to time with drops of physiologic saline solution.

In the preliminary exploratory experiments, naked eye observation of the artery was used, but in the majority of cases a Bausch and Lomb dissecting microscope with a Zeiss micrometer eyepiece was employed. Magnification in the region of 10 times was obtained and measurements could be made to two decimal places of a millimeter. No unduly bright or close source of light was necessary so that problems of heating by the light source did not arise.

Measurement of Paw Volume.—In most animals, information about the state of the peripheral circulation concomitant with large vessel changes was obtained from plethysmographs applied to the paws. These consisted of glass tubes connected to recording devices writing upon smoked paper on a kymograph. Water baths surrounded the glass tubes to nullify the effect of fluctuation in room temperature and it was endeavored to keep this as constant as possible. A record was kept of room temperature during the experiment so that effects due to any marked changes could be known and excluded. The volume of paw included in the plethysmograph was usually about 40 c.c. and an airtight seal was made between the plethysmograph and the closely clipped skin of the limb with a glue made of printer's compound. Leakage was carefully tested when the apparatus was first set up and corrected, if present.

Tourniquets.—Parts of the investigation of reflex spasm consisted of a series of tourniquet experiments on rabbits similar to those performed by Trueta and his co-workers[12, 13] and an exactly similar method of application of a rubber-covered wire tourniquet was used. After a number of experiments some disadvantages of this technique became evident: congestion of the veins of the leg always occurred, as it is impossible to tighten the wire rapidly. Furthermore, the artery lying between the femur and tuber ischii over which the wire passed is protected and arterial occlusion often did not occur at once, but only after some swelling of the limb had taken place through venous obstruction. This made uncertain the exact duration of arterial occlusion, allowed local swelling to take place before release of the tourniquet, and caused the animal to get a small transfusion of stagnant blood when the wire was released.

It was thought that a simple rubber arterial tourniquet applied to the thigh just below the tuber ischii was more simple and desirable and this was adopted for the later tourniquet experiments. An Esmarch bandage was tightly applied to the limb, before the rubber tourniquet, in order to avoid venous congestion.

Blood Pressure Records.—The carotid blood pressure was recorded during the experiments by means of a glass cannula (coated with "Dri-film" to help prevent clotting) tied into the right common carotid artery and connected by a system filled with 3 per cent sodium citrate to a mercury manometer writing upon a smoked drum.

Anesthesia.—Intraperitoneal Nembutal, supplemented by open ether when necessary, was used on the first animals in the tourniquet experiments in the same way as Trueta and his co-workers[12, 13] had used it. Nembutal acts only for about seventy-five minutes and therefore requires repetition. Open ether causes fluctuations in blood pressure and secondary effects upon the vascular system. In the later tourniquet experiments, therefore, longer acting anesthetics which gave a steadier preparation with less rapid deterioration were used. Intravenous 25 per cent urethane, 8 c.c. per kilogram body weight, was employed, or in cases where no reflex activity was being investigated, Dial-urethane,* 0.7 c.c. per kilogram intraperitoneally, was used.

EXPLORATORY EXPERIMENTS

A variety of different maneuvers was carried out and the effects observed by the naked eye on the femoral artery of both sides (see Table I). Some of these procedures were then selected for study in greater detail.

Is Large Artery Spasm Always Accompanied by Spasm of Collaterals? In most of these experiments concomitant limb volume records were made with plethysmographs on the paws. Spasm of the femoral artery produced by mechanical trauma did not affect the volume of the paw on the same side, or at least no more than simple ligature did. This finding is inconsistent with the view sometimes advanced that active spasm of the whole arterial tree follows segmental spasm of a large artery. On the other hand, decrease in limb volume did occur if the spasm extended sufficiently far along the artery to include the openings of branches.

TABLE I. RESULTS OF EXPLORATORY OBSERVATIONS

EVENT	EFFECT ON DIAMETER OF FEMORAL ARTERY (NAKED EYE OBSERVATIONS)	
	SAME SIDE	OPPOSITE SIDE
1. Mechanical trauma (longitudinal or transverse stretch, pinching, recoil, etc.)	Decrease	Nil
2. Fall in blood pressure, shock	Decrease	Decrease
3. Faradic stimulation directly to artery	Nil	Nil
4. Faradic stimulation directly to denervated artery	Nil	Nil
5. Faradic stimulation to lumbar sympathetic chain	Nil	Nil
6. Faradic stimulation to central end of sciatic nerve	Nil	Nil
7. Faradic stimulation to central end of femoral nerve	Nil	Nil
8. Faradic stimulation to femoral vein	Nil	Nil
9. Mechanically produced spasm of femoral vein	Nil	Nil
10. Ligature of femoral vein	Nil	Nil
11. Faradic stimulation directly on spastic femoral artery	Nil	Nil
12. Faradic stimulation of lumbar sympathetic (spastic femoral artery)	Nil	Nil
13. Galvanic stimulation directly to artery	Dilatation	Not observed

How Does the Behavior of Other Large Arteries Compare With the Femoral? The effects of some of the factors listed in Table I were also observed in large arteries other than the femoral. Repetitive electric stimuli of various

*Manufactured by Ciba Pharmaceutical Products, Inc., Summit, N. J.

characteristics were applied to the upper and lower abdominal aorta, the carotid, and the iliac arteries of rabbits and cats. In no case was significant narrowing observed.

Response to mechanical trauma such as that produced by a sharp jerk with a thread placed under the artery is recorded in Table II for different arteries. Sections of these arteries were removed from the animals and examined microscopically after staining with hematoxylin and eosin or Masson's stain. The amount of elastic and fibrous tissue present in proportion to muscle was much greater in the arteries in which spasm was difficult to produce. Complete occlusion by traumatic spasm could not be produced at all in the aorta which has a high proportion of fibrous tissue. It also has a high blood pressure, a factor which was studied more closely in the detailed experiments.

It is interesting to note that John Hunter[14] observed that the larger arteries of the cow's placenta contracted less easily than the smaller ones.

DETAILED EXPERIMENTS

Factors affecting arterial diameter which were chosen for more detailed study fell under two headings: (1) those acting directly upon the vessel, such as changes in blood pressure, mechanical trauma, or the possible effect of vasomotor nerves; (2) nervous factors acting reflexly from other parts of the body.

The first group was studied in both cats and rabbits using the techniques already described of direct observation of the diameter of the femoral artery with concomitant limb volume records by plethysmographic means.

Reflex arterial spasm was studied particularly in rabbits in a series of tourniquet experiments in each of which the behavior of the right femoral artery

TABLE II. PRODUCTION OF SPASM BY MECHANICAL MEANS IN VARIOUS ARTERIES OF THE RABBIT AND THE CAT

EASE OF ELICITING SPASM	ARTERY
1. Produced easily	Femoral; brachial
2. Produced with slight difficulty	External iliac; common iliac
3. Produced with great difficulty	Abdominal aorta; common carotid

and limb volume was studied in response to a tourniquet applied to the left thigh. This was done first on animals with an intact nervous system and later on animals in which parts of possible nervous reflex pathways had been excised.

Influence of the Blood Pressure on the Diameter of Large Arteries.—It was noticed quite early in these investigations that arteries became gradually smaller during the course of the experiment as the animal's condition deteriorated and that finally, when the blood pressure was low, the vessels were very narrow indeed. This happened just as constantly in animals in which the lumbar sympathetic chains and arterial adventitia had been removed as in those in which the nervous system was intact. These gradual changes in diameter were studied in greater detail in the tourniquet experiments which will be described later.

The effects of more rapid variation in blood pressure upon the artery, produced by a variety of agents, were studied. Intravenous injections of

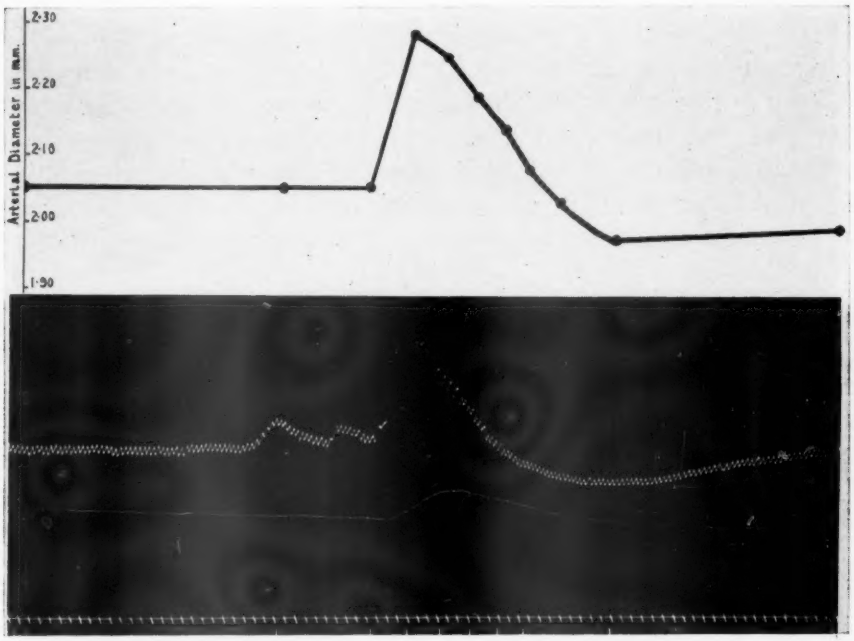

Fig. 1.—Cat anesthetized with intraperitoneal dial (Ciba; 0.7 c.c. per kilogram). Injection of 1 c.c. of 1:25,000 adrenalin at third signal. Records from above down: diameter of right femoral artery, carotid blood pressure, volume of right hind paw, time signals at ten second intervals. All other signals refer to points at which arterial diameter was measured. Changes in the arterial diameter follow the blood pressure.

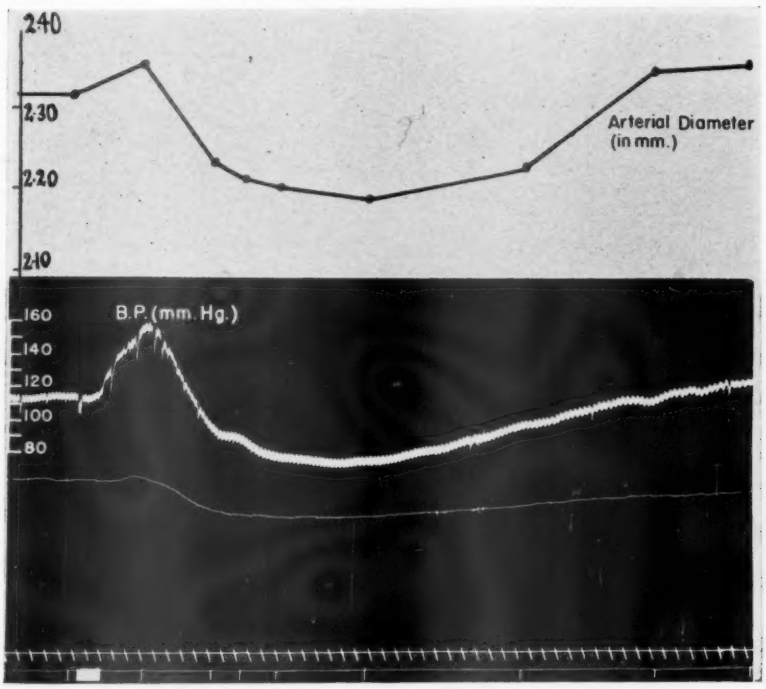

Fig. 2.—Cat anesthetized with urethane (8 c.c. of 25 per cent solution intravenously). Right lumbar ganglionectomy one hour previously. Intravenous injection of 1 c.c. of 1:25,000 adrenalin at second signal. Records as in Fig. 1.

adrenalin producing a rise in blood pressure caused a parallel increase in diameter of the artery. This occurred in both the intact and sympathectomized limb (see Figs. 1, 2, and 3). The limb volume shrinks in a sympathectomized limb but swells in the intact one following adrenalin injection. In the latter case the vessels are presumably constricted to start with and the increase in limb volume is purely passive. Faradic stimulation of the central part of the cut brachial plexus produced a reflex rise in blood pressure and the diameter of the artery was seen to enlarge simultaneously and shrink to its former size as the blood pressure fell once more (Fig. 4).

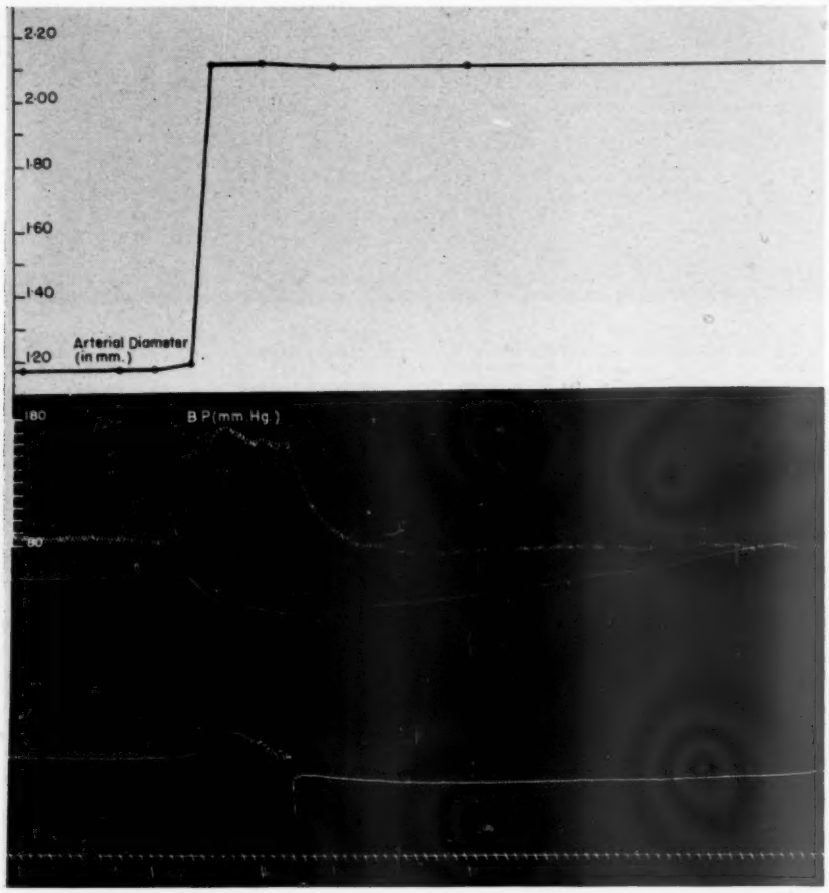

Fig. 3.—Cat anesthetized with dial as in Fig. 1. Right lumbar preganglionic section three hours before. Adrenalin 0.5 c.c. (1:25,000) intravenously (signals 3 to 4). Records from above down; diameter right femoral artery, carotid blood pressure, right (sympathectomized), and left (intact) limb volumes. All other signals refer to points at which arterial diameter was measured. This illustrates release of the "ratchet" mechanism of smooth muscle fibers which sometimes take up a new resting length with large increases in blood pressure.

Fluctuations in blood pressure due to the administration of open ether caused parallel changes in arterial diameter. Fig. 5 shows how the diameter decreased when fall in blood pressure occurred after administration of open ether.

Intravenous injections of Nembutal produced a fall in blood pressure with parallel narrowing of the artery (see Fig. 6). The pressure and diameter

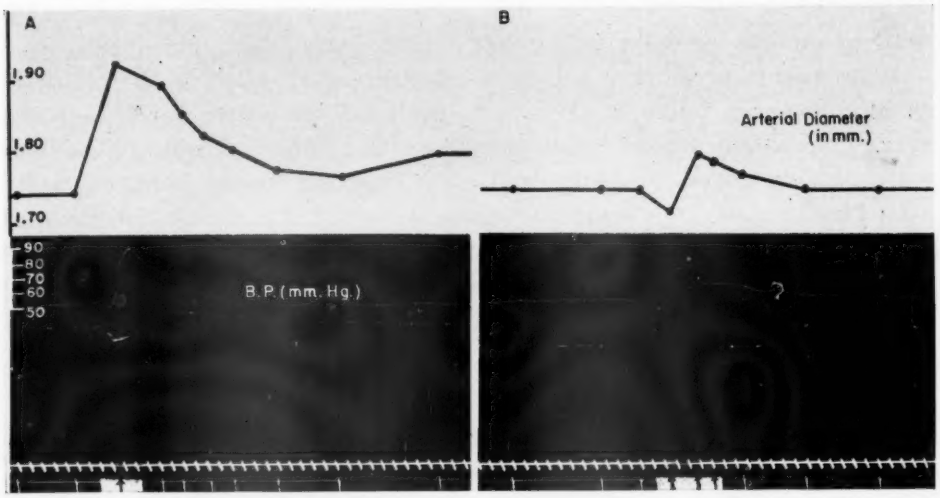

Fig. 4.—Rabbit anesthetized with urethane (8 c.c. of 25 per cent solution intravenously). *A*, 8 volts in primary; *B*, 3½ minutes after *A*, 4 volts. Secondary coil (Harvard inductorium) at 8 cm. Adrenals intact. Order of records as in Fig. 1. Faradic stimulation of brachial plexus centrally causing reflex blood pressure changes. The diameter of femoral artery follows the change in blood pressure.

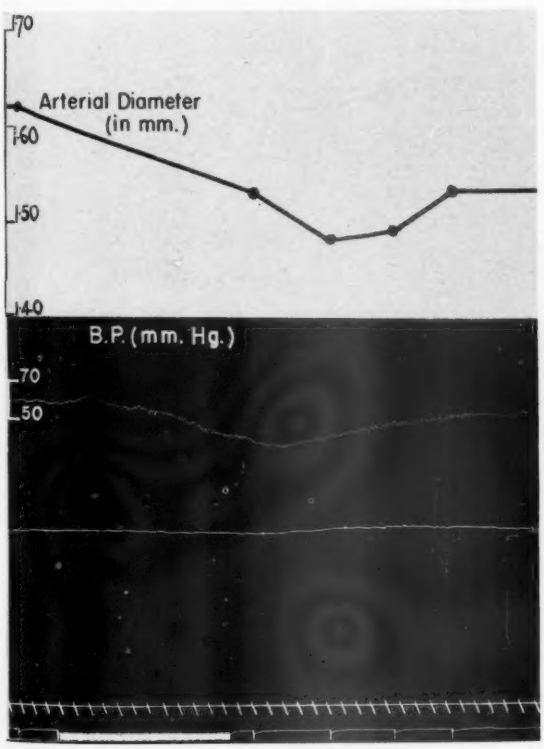

Fig. 5.

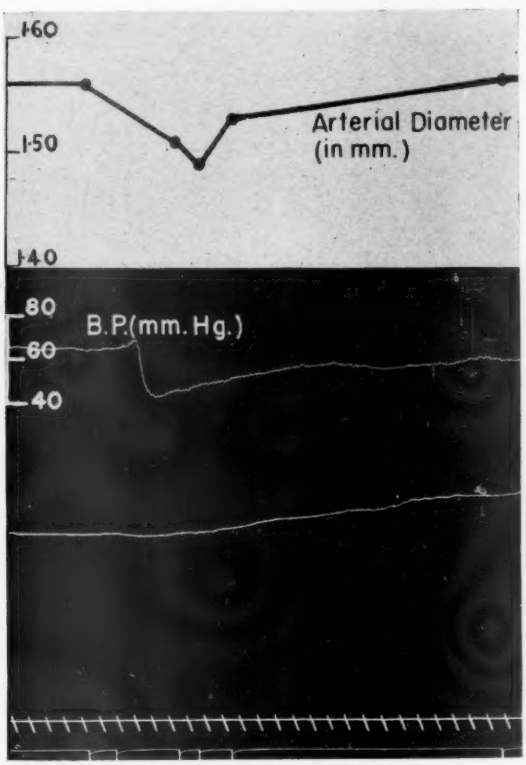

Fig. 6.

Fig. 5.—Rabbit anesthetized with intraperitoneal Nembutal (0.4 c.c. per kilogram). Dilute ether vapour by inhalation at long signal. All other signals refer to points at which arterial diameter was measured. The blood pressure falls and the femoral artery shrinks.

Fig. 6.—Rabbit anesthetized with Nembutal (0.4 c.c. per kilogram intraperitoneally). Further injection of Nembutal intravenously (15 mg.) at second signal. Order of records as in Fig. 1. Blood pressure and femoral arterial diameter both decrease.

variations occurring with ether and Nembutal influenced our choice of anesthetic agents for the later tourniquet experiments.

Other agents producing a fall in blood pressure, such as Priscol or injections of adrenalin following Priscol,* produced the same fall in arterial diameter. The changes in arterial diameter with all the different drugs or mechanisms altering blood pressure indicated that the vessel behaved passively like an elastic tube. On some occasions, however, a somewhat different type

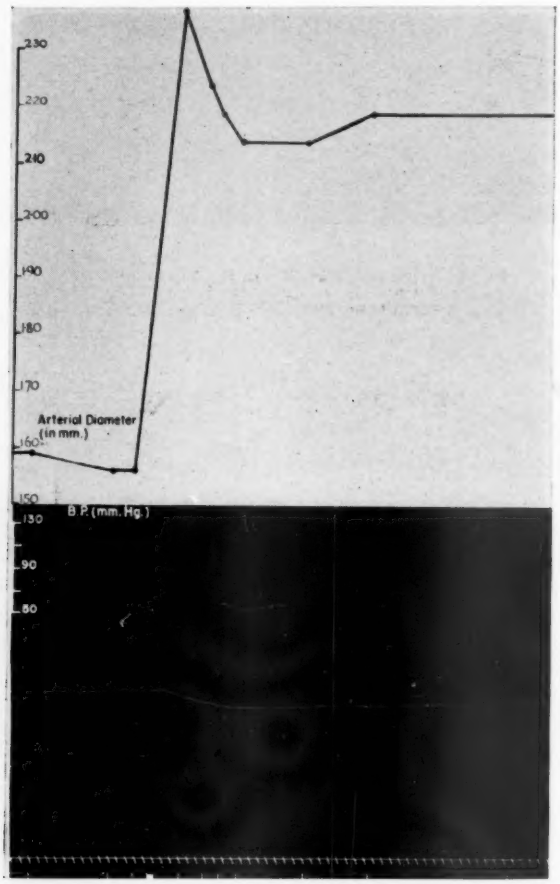

Fig. 7.—Rabbit anesthetized with Nembutal intraperitoneally (0.4 c.c. per kilogram). Adrenalin 0.5 c.c. intravenously at fourth signal. Order of records as in Fig. 1. This illustrates release of the "ratchet" mechanism of smooth muscle fibers which sometimes take up a new resting length with increase in blood pressure.

of change occurred: in response to pronounced or prolonged rises in blood pressure produced by slow intravenous administration of adrenalin, the artery rapidly dilated to almost twice its former diameter and remained at this size, varying by the usual amounts from this new diameter with subsequent blood pressure variations (see Figs. 3 and 7). This suggested that the muscle fibers had taken up a new resting length and that some mechanism similar to the "ratchet" mechanism of bivalves had been released.

Nervous Control of Large Artery Diameter.—Electric stimulation of the lumbar sympathetic and of the artery itself was used to attempt to dem-

*Furnished by Ciba.

onstrate changes in diameter. The blood pressure was recorded in all these experiments in order to exclude diameter changes due to its variation. The lumbar sympathetic trunk was isolated and divided as high as possible where it first appeared in the abdomen from under cover of the diaphragmatic crus. Electrodes were placed under the chain just below this point of section, the abdomen closed, and the blood pressure allowed to stabilize. This high position on the chain was chosen to ensure that stimulation occurred from the first and second lumbar ganglia, which might supply fibers to the femoral artery, downward. Repetitive electric stimulation with an electronic stimulator* was then applied in voltages varying from 2 to 20, usually using a biphasic current of 0.5 to 2.0 milliseconds duration at a frequency of 30 per second. Effective sympathetic stimulation was evident in the rabbit and cat by

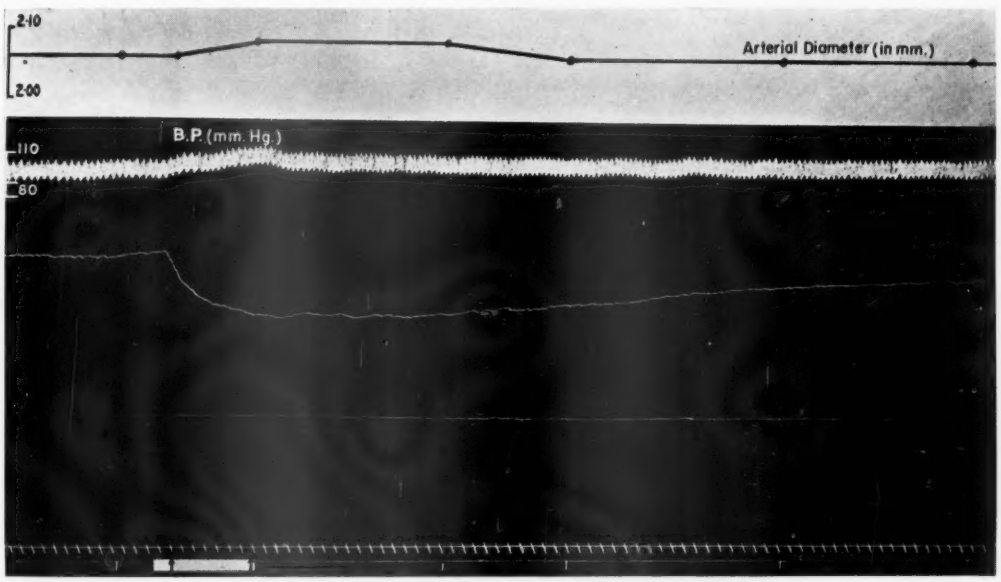

Fig. 8.—Cat anesthetized with urethane (8 c.c. of 25 per cent solution intravenously). Long signal: electric stimulation of right sympathetic chain in region of first lumbar ganglion (10 volts biphasic, duration 1 millisecond, frequency 30 per second). The right femoral arterial diameter increases very slightly with the blood pressure. The right leg volume shrinks. Left leg volume (lowest record) unchanged.

shrinkage of the volume of the limb in the plethysmograph and also in the cat by erection of the hairs of its tail. In no case was any diminution in the diameter of the femoral artery observed (see Fig. 8). Identical results were obtained in both the rabbit and cat. The femoral artery was also stimulated directly with similar repetitive stimuli using electrodes held in contact with the artery on a rigid stand which prevented any movement likely to cause mechanical trauma. Upon no occasion did any change in diameter attributable to the electric stimulus occur. In these experiments the adventitia and periarterial tissue had been left in situ (Fig. 9).

These results indicate an absence of vasomotor fibers controlling the femoral arteries, and similar experiments, already mentioned, upon other large vessels were in agreement.

*Manufactured by the Grass Instrument Company.

MacWilliam[10] found that stimulation with a strong galvanic current caused some contraction of pieces of ox artery in vitro. Using the same technique as before, we applied galvanic stimuli to the femoral arteries of rabbits varying the strength from 4 to 11 volts. A marked local dilatation of the artery took place in the region of the electrodes. The dilatation took some one-half to one minute to occur and subsided rapidly when the current was stopped. The degree of dilatation was larger with higher voltages but quite definite at 4 volts. It was repeated several times, both on vessels with intact adventitia and on vessels with the adventitia removed. The response was the same in either case, suggesting that nervous factors played no part in the phenomenon.

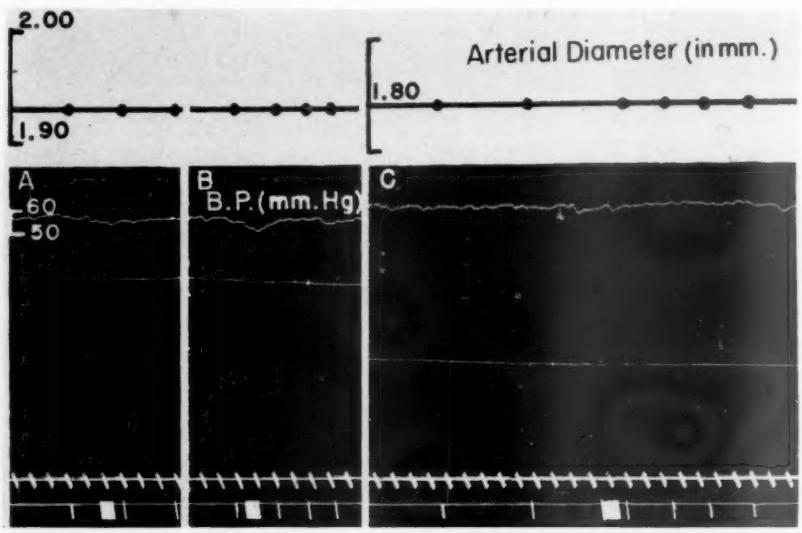

Fig. 9.—Rabbit anesthetized with urethane intravenously (8 c.c. of a 25 per cent solution per kilogram). Repetitive electric stimulation applied directly to right femoral artery at long signals. *A*, 6 volts, frequency 25 per second, duration 1 millisecond. *B*, 8 volts, frequency 30 per second, duration 1 millisecond. *C* (11 minutes after *B*), 10 volts, frequency 30 per second, duration 1 millisecond. All other signals refer to points at which arterial diameter was measured.

Response to Mechanical Trauma.—In contrast to the negative responses to nerve stimulation, mechanical trauma easily produced spasm in the femoral artery of the rabbit or cat. Longitudinal stretching of a segment, transverse stretching by means of fine dissecting forceps, or pinching, all produced it constantly. Rapid stretching was more effective than slow. A method which gave a constantly repeatable stimulus without damaging the vessel was that obtained by giving the vessel a sharp jerk at right angles with a length of cotton thread passed under it. This produced spasm of a segment of artery which came on in a slow and wormlike fashion; the lumen became occluded and pulsation disappeared. This spasm gradually wore off if the vessel was left undisturbed and by the end of one hour the vessel usually returned to its initial diameter. Similar behavior was observed in vessels denervated by removal of the adventitial coat. Immediately after relaxation further stretching was found to produce little or no response. The muscle fibers were re-

fractory and further stimulation sometimes even produced localized fusiform dilatation similar to that described by Grant[11] in the rabbit's ear.

Reflex Spasm of Large Arteries.—Barnes and Trueta,[12] working with rabbits, demonstrated a shrinkage of the arterial tree of the hind leg on the side opposite to that on which a tourniquet had been in place for a time greater than an arbitrary period of four and a half hours. Injection of thorotrast into the abdominal aorta and radiography were used to outline the vessels of the hind legs. Trueta and associates[13] used similar techniques and concluded that the distant vascular effects were due to nervous reflex mechanisms.

A series of tourniquet experiments was performed to examine the question of "reflex" spasm more closely and some aspects of these have been alluded to previously under the heading of Methods. Records of the hind-limb volumes, blood pressure, and right femoral artery diameter were begun about one-half hour before release of the tourniquet which was applied, as a convenient routine, always to the left thigh. The diameter records and the records of limb volume and blood pressure on the smoked drum were afterward represented on paper in graphic form for each animal. Fig. 10 is an example of the typical pattern found in the animals with intact nervous system and Fig. 11 is an example of that found in animals in which bilateral lumbar sympathectomy (L_1 through S_2 or S_3) and local periarterial denervation of the right femoral artery had been performed. Shrinkage of the contralateral leg and of the femoral artery occurred in both groups as did a fall in blood pressure.

Table III summarizes the findings in animals with intact nervous systems and Table IV summarizes those in which the pathways had been interrupted.

COMMENTS ON TABLE III (TOURNIQUET EXPERIMENTS ON INTACT ANIMALS)

Anesthesia.—Nembutal (sometimes with the addition of open ether) was used in the first 11 cases. Rapid deterioration was found to occur. This anesthesia was used because it was desired to repeat exactly the technique of Barnes and Trueta.[12] A change was made to urethane in the later experiments in order to produce a more stable preparation and one which did not deteriorate so rapidly.

Regardless of the anesthetic used, the relation between changes in contralateral leg volume and arterial diameter and changes in blood pressure remained constant.

Type of Tourniquet.—With one exception, all animals in which a wire tourniquet was used developed congestion of the limb which shrank after removal of the wire.

Contralateral Leg Volume.—Shrinkage occurred in all cases but 3. In two of these three cases, the blood pressure remained at a high level during the period of observation.

Right Femoral Artery Diameter.—In all cases observed, the right femoral artery diameter diminished during the period of observation, except in one case (animal 9).

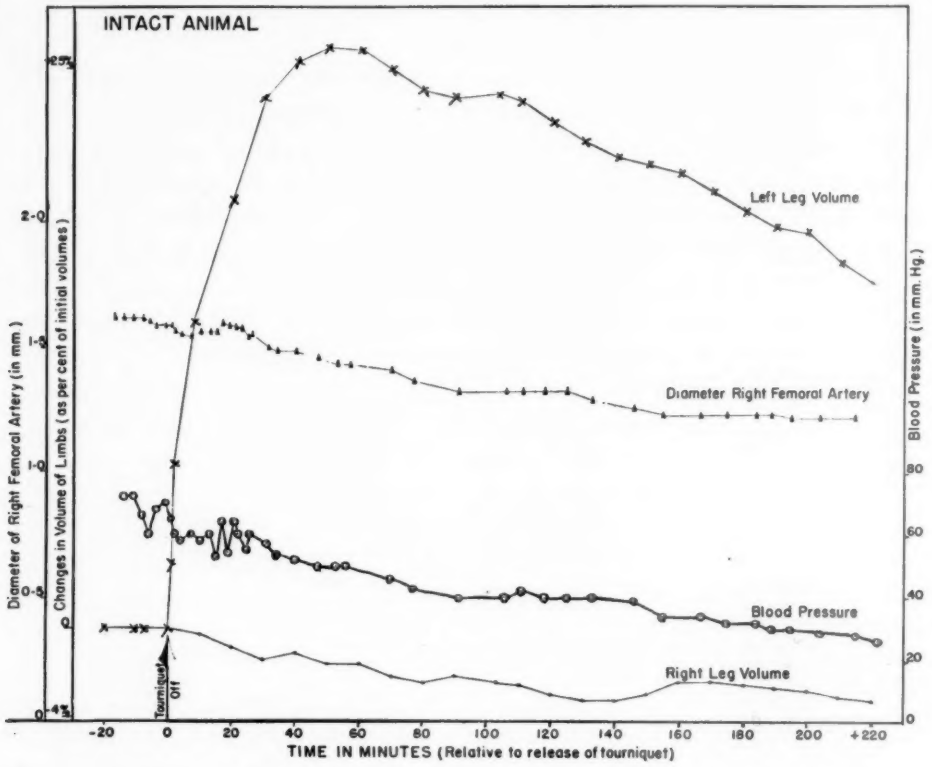
INTACT ANIMAL
Left Leg Volume
Diameter Right Femoral Artery
Blood Pressure
Right Leg Volume
Tourniquet Off
Diameter of Right Femoral Artery (in mm.)
Changes in Volume of Limbs (as per cent of initial volumes)
Blood Pressure (in mm. Hg.)
TIME IN MINUTES (Relative to release of tourniquet)

Fig. 10.—Rabbit anesthetized with urethane as in previous experiments. Nervous system intact. Rubber arterial tourniquet for five and one-fourth hours, left thigh. Decline in right femoral artery diameter, leg volume and blood pressure. (Animal 15 in Table III.)

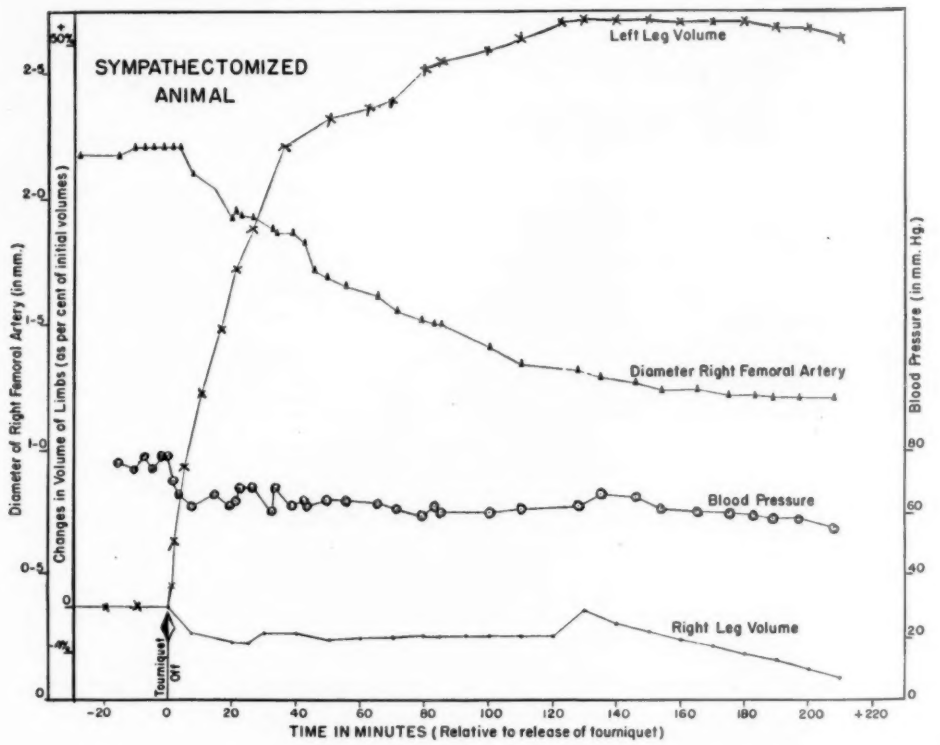
SYMPATHECTOMIZED ANIMAL
Left Leg Volume
Diameter Right Femoral Artery
Blood Pressure
Right Leg Volume
Tourniquet Off
Diameter of Right Femoral Artery (in mm.)
Changes in Volume of Limbs (as per cent of initial volumes)
Blood Pressure (in mm. Hg.)
TIME IN MINUTES (Relative to release of tourniquet)

Fig. 11.—Rabbit anesthetized with urethane anesthesia as in previous experiments. Acutely sympathectomized hindlimbs. Rubber tourniquet released after five hours on left thigh. Pattern of events is similar to intact animal (see Fig. 10), except that swelling of left leg is approximately twice as great. (Animal 10 in Table IV.)

TABLE III. TOURNIQUET EXPERIMENTS (ANIMALS WITH INTACT NERVOUS SYSTEM)

NO.	ANESTHESIA	TOURNIQUET		CHANGE IN LEG VOLUME		CHANGE IN DIAMETER OF RIGHT FEMORAL ARTERY (MM.)			BLOOD PRESSURE (MM. HG) DURING PERIOD OF OBSERVATION			
		TYPE	DURATION (HR.)	RIGHT	LEFT (TOURNIQUET SIDE)	INITIAL	FINAL	RANGE	INITIAL	FINAL	RANGE	PERIOD OF OBSERVATION (MIN.)
1	Nembutal and ether	Wire	7	Fall	Fall	NR*	NR	NR	78	56	22	48
2	Nembutal and ether	Wire	6½	Fall	Fall	NR	NR	NR	80	58	22	18
3	Nembutal and ether	Wire	6⅔	Fall	Fall	NR	NR	NR	38	44	6	65
4	Nembutal and ether	Wire	6⅔	Fall	Fall	NR	NR	NR	70	10	60	30
5	Nembutal and ether	Wire	5½	Fall	Fall	NR	NR	NR	55	55	0	35
6	Nembutal and ether	Wire	4½	Fall	Fall	NR	NR	NR	78	26	52	58
7	Nembutal and ether	Wire	3¾	Nil	Rise	1.47	1.34	.13	102	78	24	70
8	Nembutal and ether	Wire	7	Fall	Fall	2.00	1.59	.41	73	24	49	100
9	Nembutal and ether	Wire	6	Fall	Fall	1.62	1.62	–	70	72	2	64
10	Nembutal and ether	Wire	3¾	Nil	Fall	2.36	2.17	.19	112	102	10	80
11	Nembutal and ether	Wire	7	Fall	Fall	2.15	1.90	.25	NR	NR	NR	130
12	Urethane	Rubber†	5¼	Fall	Rise	1.21	1.14	.07	72	60	12	115
13	Urethane	Rubber	5¾	Nil	Rise	1.97	1.56	.41	100	20	80	335
14	Urethane	Rubber	5¾	Fall	Rise	1.35	1.15	.20	64	38	26	207
15	Urethane	Rubber	5¼	Fall	Rise	1.61	1.21	.40	72	28	44	229

*NR is abbreviation for not recorded.
†Rubber arterial tourniquet preceded by Esmarch bandage.

TABLE IV. SYMPATHECTOMIZED OR DENERVATED ANIMALS

NO.	ANES-THESIA	TOURNIQUET		CHANGE IN LEG VOLUME		CHANGE IN DIAMETER OF RIGHT FEMORAL ARTERY (MM.)			BLOOD PRESSURE (MM. HG) DURING PERIOD OF OBSERVATION				STATE OF NERVOUS SYSTEM
		TYPE	DURATION (HR.)	RIGHT	LEFT (TOURNIQUET SIDE)	INITIAL	FINAL	RANGE	INITIAL	FINAL	RANGE	PERIOD OF OBSERVATION (MIN.)	
1	Nembutal	Wire	5¼	Fall	Fall	1.37	1.07	.30	64	30	34	145	Denervated left limb
2	Nembutal	Rubber	6	Fall	Rise	1.66	1.19	.47	85	46	39	76	Denervated left limb
3	Urethane	Rubber	8	Rise	Rise	2.02	1.71	.31	96	36	60	292	Chronically sympathectomized
4	Urethane	Rubber	6¾	Fall	Rise	1.27	1.27	0.00	20	18	2	74	Chronically sympathectomized
5	Urethane	Rubber	4	Nr	NR	1.26	1.24	.02	72	0	72	30	Chronically sympathectomized
6	Urethane	Rubber	5	Fall	Rise	1.51	1.12	.39	50	17	33	47	Acutely sympathectomized
7	Dial	Rubber	2¾	NR	NR	1.35	1.20	.15	70	26	44	96	Chronically sympathectomized
8	Urethane	Rubber	2½	Fall then rise	Rise	1.46	1.02	.44	60	20	40	197	Acutely sympathectomized
9	Urethane	Rubber	6¼	Fall	Rise	1.85	1.50	.35	66	30	36	202	Acutely sympathectomized
10	Urethane	Rubber	5	Fall	Rise	2.21	1.21	1.00	78	55	23	220	Acutely sympathectomized

Blood Pressure.—The blood pressure fell during the period of observation in almost every case. Most of the animals with a rubber tourniquet showed an acceleration in the rate of fall just after removal of the tourniquet. This was not noticeable when a wire one was used presumably because the rabbit received a small transfusion from the distended veins when the wire was removed.

Period of Observation.—The period of observation referred to in the last column was that time during which good blood pressure, leg volume, and arterial diameter observations were made, usually from a few minutes before the release of the tourniquet until the animal died or showed marked signs of deterioration, although some of the earlier experiments were discontinued before this occurred.

COMMENTS ON TABLE IV

Cases 1 and 2 were animals in which all the somatic nerves of the left hindlimbs had been divided at points where they left the pelvis, one week before applying the tourniquet to the left thigh. The object was to see whether removal of these afferent pathways of a possible reflex arc would influence the shrinkage of limb volume and arterial diameter upon the opposite side. It did not do this in either animal.

In the remaining eight cases (animals 3 to 10) which had been sympathectomized, it was found that:

1. The *contralateral limb volume* shrank in four, rose in one, fluctuated in another, and in two was not recorded, owing to the poor condition of the animals.

Most showed minor fluctuations, often in the opposite direction to the blood pressure, which were not noticed in the intact animals. This is in line with the observations of Dole and Morison[15] on sympathectomized and denervated limbs when investigating vasodilator action.

2. *Diameter of Right Femoral Artery.* The diameter shrank in six out of eight cases following the trend of the blood pressure. Of the remaining two cases, one had a very low blood pressure (20 mm.) at the start, and the other animal died almost at once upon release of the tourniquet.

3. *Blood Pressure.* A general downward trend occurred during the period of observation going parallel with the shrinkage of the contralateral femoral artery.

Summarizing the findings in the tourniquet experiments, it is concluded that shrinkage of the artery and contralateral limb volume most certainly took place, but that it occurred (with minor differences in leg volume change) in both the intact animals and in those which had denervated or sympathectomized limbs. The shrinkage of the artery went along with a falling blood pressure, and in no case were abrupt changes observed such as might have been expected from the activation of a nervous reflex. Figs. 12 and 13 are portions excised from the records of an intact and a sympathectomized animal, respectively, showing the events which occurred on release of the tourniquet. No abrupt changes were evident such as might be expected were a nervous

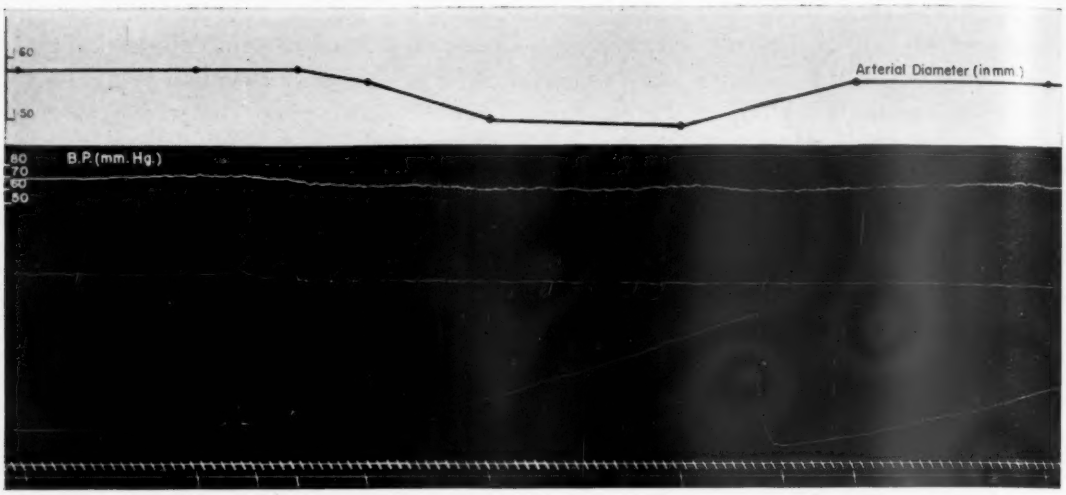

Fig. 12.—Rabbit with intact nervous system. Urethane used as in previous experiments. Release of rubber tourniquet after five and one-fourth hours on left thigh, at third signal. Records from above down: diameter right femoral artery, carotid blood pressure, right hind leg volume, left hind leg volume. All other signals refer to points at which arterial diameter was measured. The left leg swells rapidly, necessitating readjustment of plethysmograph recording lever. No abrupt changes on right side, although diameter and volume subsequently declined with fall in blood pressure. (This is Rabbit 15 in Table III.)

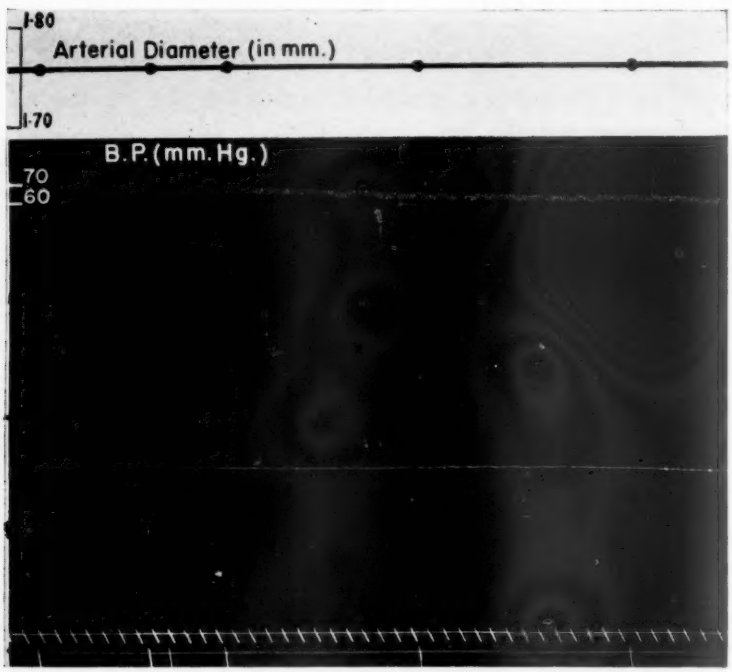

Fig. 13.—Rabbit anesthetized with urethane intravenously as in preceding experiments. Acutely sympathectomized hindlimbs. Rubber arterial tourniquet released from left thigh (after six and one-fourth hours) at second signal. Records from above down: femoral artery diameter; volume of right (sympathectomized) hindlimb; volume of left (intact) forelimb. (Animal 9 in Table IV.) All other signals refer to points at which arterial diameter was measured.

reflex activated. The usual gradual downward trends in arterial diameter and contralateral leg volume occurred in both intact and sympathectomized animals as the blood pressure fell subsequently.

DISCUSSION

Spasm of the large arteries resulting from trauma has been recognized for many years, and its clinical significance has been emphasized. Of great interest have been the reports of arterial spasm following trauma to the contralateral limb. Barnes and Trueta[12] have presented arteriographic evidence and suggested that this contralateral arterial spasm occurs as a result of a nervous reflex. Because of the clinical and physiologic implications it was thought desirable to reinvestigate the problem of "reflex spasm" in the large arteries.

On the basis of available evidence (Moore and Moore,[16] Moore and Singleton,[17] and Simeone and Watkins[18]) reflex effects from irritation of large arteries would not be expected. The radiographic data obtained by Barnes and Trueta were recorded some time after release of the tourniquet. During this lapse of time, possible changes in the arterial blood pressure of the animals, which per se might have affected the caliber of the arteries, were not recorded. They used light nembutal anesthesia supplemented with ether when needed. The possible effects of supplementary anesthesia itself on arterial caliber were not controlled. The technique of arteriography involved celiotomy and aortic puncture. The possible effects of these procedures themselves upon an animal which is deteriorating after hours of anesthesia require control.

The results of experiments recorded in this report indicate that changes in the diameter of the femoral artery do occur after release of the tourniquet (Figs. 10 and 11). However, it appears that these changes are purely passive. In the first place, the diameter of the artery varies in direct proportion with the systemic arterial blood pressure. Rises in blood pressure, obtained by whatever means, are attended by an increase in the diameter of the femoral artery (Figs. 1 and 4). Falls in systemic blood pressure, by whatever methods produced, are attended by a shrinkage of the femoral artery (Figs. 2, 5, and 6). Furthermore, these changes in diameter of the femoral artery occur regardless of whether the systemic nerves or the sympathetic nerves to the limb are intact or ablated (Tables III and IV; Figs. 10 and 11). Indeed, Fig. 13 shows that in this particular rabbit the slight fall in blood pressure associated with release of the tourniquet was attended by a shrinkage in the sympathectomized paw (upper plethysmographic record) without any shrinkage in the normally innervated paw (lower plethysmographic record). Had a reflex been produced by removal of the tourniquet one would have expected a greater change in the normally innervated limb than in the sympathectomized limb.

The experiments reported in this paper have further tested the concept of reflex spasm in large arteries by tests on the efferent segments of the possible reflex arc. Stimulation of the decentralized lumbar ganglionated trunk produced plethysmographic shrinkage of the paw without shrinkage of the

femoral artery (Fig. 8). Direct electric stimulation of the femoral artery and its adventitia produced no change in the caliber of this vessel (Fig. 9). If the femoral artery were a part of a reflex arc one would expect that these procedures would affect its caliber. These observations are in accord with the findings of MacWilliam[10] on excised arterial segments and with those of Rosenblueth and Cannon[19] on the denervated nictitating membrane.

That the criticism of the administration of additional anesthetic agent during the experiment is reasonable, is demonstrated by Figs. 5 and 6, which indicate that both nembutal and ether may themselves produce a change in the diameter of the femoral artery as a result of their effect on the systemic blood pressure.

The experiments reported here suggest that while the femoral artery is not under the direct control of the nervous system, it can alter its size on a myogenic basis (stretch) and as a passive reflection of the systemic blood pressure.

A curious phenomenon was observed during the course of these experiments. Following positive stretching of the artery by a rise in systemic blood pressure induced by adrenalin, the wall of the artery suddenly relaxed and assumed a new resting position (Figs. 3 and 7), reminiscent of the mollusc adductor with its "ratchet device." The behavior of the arterial diameter subsequently followed the various stimuli in the usual manner but from its new resting level.

CONCLUSIONS

1. Local segmental spasm in the large arteries can be produced by mechanical trauma, irrespective of the presence of the adventitia and possible nerve supply.

2. Electric stimulation of the sympathetic nerve supply to the limb or of the artery and its adventitia directly has failed to reveal evidence of nervous motor control of the large arteries.

3. After release of a tourniquet applied to the thigh for two and one-half to seven hours, there is a demonstrable shrinkage of the contralateral femoral artery.

4. The shrinkage of the femoral artery develops slowly and not abruptly after removal of the tourniquet from the contralateral thigh.

5. The observed shrinkage of the femoral artery is a consequence of the gradual fall in blood pressure and not a result of reflex activity.

6. The caliber of the large arteries follows passively the systemic blood pressure; it increases with rises in blood pressure and decreases with falls in blood pressure, howsoever these are produced.

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AN EXPERIMENTAL STUDY OF CARDIAC MASSAGE

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DURING the treatment of patients with cardiac arrest, some of whom were recently reported upon,[1] the authors have been uncertain about the rate at which the heart should be compressed. A review of the literature reveals a difference of opinion. Bost,[2] in analyzing the seventy-five cases of attempted cardiac resuscitation recorded before 1923, stated that it was "pretty well agreed that gentle compression of the heart should be carried out at about half the normal rate to allow the heart to fill well." Lee and Downs[3] added twenty-four cases to those collected by Bost and recommended massage at a rate of "20 times a minute, for when it resumes its beat it will start slowly." Barber and Madden[4] reviewed the world literature in 1944 and suggested a rate approximately one-half the normal or 40 or 50 times per minute. They stated that a slow rate allowed a more complete filling of the heart with an increase in the stroke and minute volume output. No data were presented in support of this statement. Ruzicka and Nicholson[5] considered 40 times a minute to be the optimal rate, while Crafoord[6] reported that he used about the same rhythm as the normal heartbeat.

Since there have been no experimental studies, to our knowledge, of the relationship between the rate of manual cardiac compression and the artificial circulation produced, the answer to this and to certain related problems were sought in the experiments herein described. The rate of blood flow was considered to be the best criterion of the efficacy of cardiac massage.

EXPERIMENT METHODS

The instrument used to measure blood flow was the bubble meter of Dumke and Schmidt.[7] This instrument has been found to be accurate and dependable, with no appreciable resistance to the blood flow even of small arteries (coronary) and no marked deviations resulting from changes in blood viscosity.[8]

Mongrel dogs averaging about 10.0 kilograms in weight were anesthetized with ether. An intratracheal tube was inserted and connected to an intermittent positive pressure apparatus delivering an air-ether mixture. The femoral vein was cannulated for the administration of intravenous fluids, and the mean arterial pressure was recorded through a cannula in a carotid or femoral artery.

In experiments measuring the blood flow through the thoracic aorta, the left chest was opened through the fifth intercostal space, and in some animals the adjacent costal cartilages were divided in addition to increase exposure. Hemostasis was made as complete as possible to minimize oozing following heparinization. The aorta distal to the subclavian artery was mobilized by reflecting the

Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 24-26, 1949.

parietal pleura and dividing and ligating four to six intercostal arteries. The animal was then heparinized, using 1.0 mg. per kilogram of body weight. Non-crushing clamps were applied proximally and distally, and the aorta was partially divided. Glass cannulas approximately the diameter of the aorta were inserted and secured with heavy silk ligatures. The glass cannulas were connected to the bubble meter by rubber tubing, the entire system having been filled with physiological saline solution. When the clamps were removed, all of the blood flowing through the descending aortic arch passed through the bubble meter (Figs. 1 and 2). Following removal of the clamps the blood pressure usually dropped from 20 to 60 mm. of mercury. After waiting for the blood pressure to return to its maximum level and become stabilized, recordings were taken of the rate of blood flow resulting from spontaneous cardiac activity. The heart was then stopped by the rapid intravenous injection of 10.0 to 15.0 c.c.

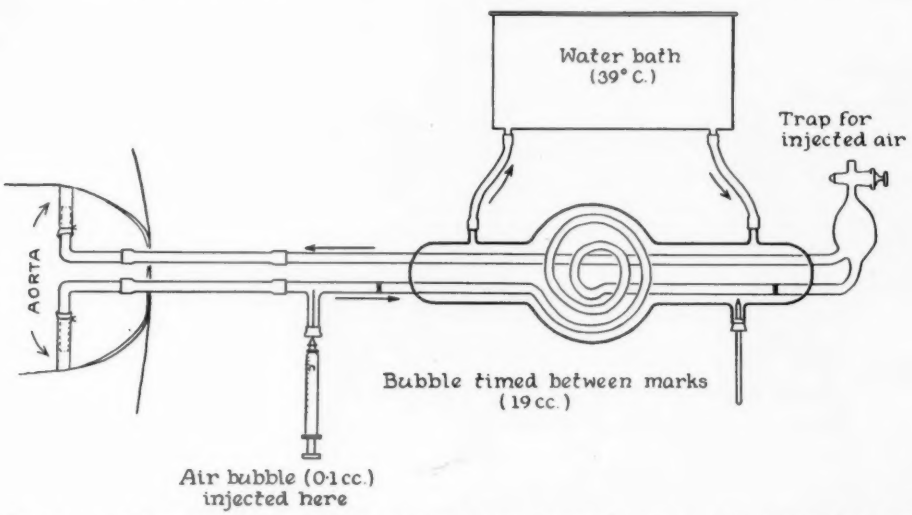

Fig. 1.—A diagram of the bubble meter in a dog's thoracic aorta. All of the blood flowing through the descending thoracic aorta passed through the bubble meter. The rate of blood flow was determined by measuring the time required for an air bubble to pass between the measuring marks on the inflow arm of the bubble meter.

of a saturated solution of magnesium sulfate, and cardiac massage was begun at a rate of 60 times per minute. The ether valve in the positive pressure apparatus was shut off, and room air was used for ventilation of the lungs during the remainder of the experiment. Blood flow through the bubble meter was recorded at frequent intervals, with varying rates of cardiac compression and relaxation and of intravenous administration of blood and physiologic saline solution. In most instances the experiment was terminated within forty-five minutes after stopping the heart because unless adequate blood was given there was significant depletion of the blood volume due to oozing from raw surfaces.

In experiments measuring the blood flow through the carotid artery the left side of the chest was opened and the animal was herparinized before inserting cannulas, connected to the bubble meter, into the carotid artery. After recordings of the carotid blood flow due to spontaneous cardiac activity were taken,

the heart was stopped, as before, and cardiac massage was begun at the rate of 60 times per minute. Frequent recordings of the carotid blood flow were then taken with and without the thoracic aorta occluded by a nonerushing clamp, with varying rates of cardiac compression, and with varying rates of blood and physiologic saline solution injected intravenously.

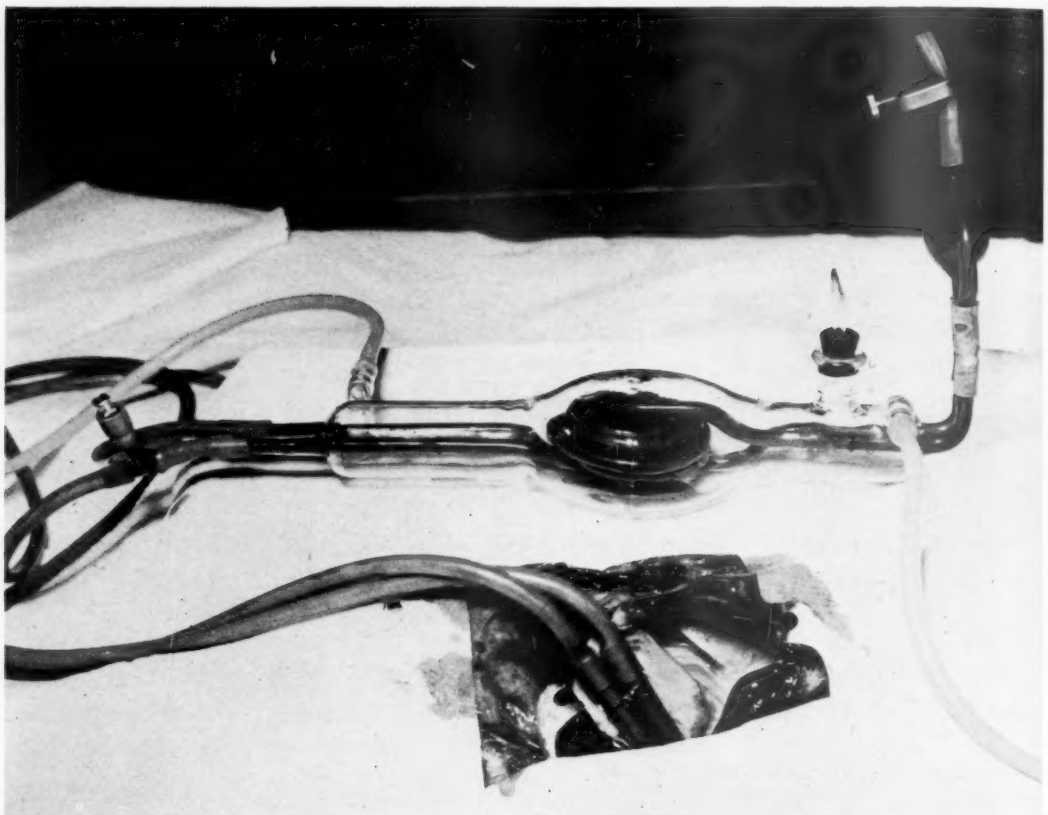

Fig. 2.—A photograph taken during one of the experiments. The cannulas in the thoracic aorta are seen in the chest incision. The heart is beating spontaneously and blood is flowing through the bubble meter.

RESULTS

Effect of the Rate of Cardiac Compression on Blood Flow.—In Table I the rate of blood flow in the thoracic aorta (six experiments) and in the carotid artery (three experiments) is shown at different rates of cardiac compression. The figures shown are the average of many consecutive recordings at 30, 60, and 120 compressions per minute. A smaller number of recordings at 45 and 90 times a minute fell between the rates of flow at 30 to 60 and 60 to 120 times per minute. Up to a rate of 120 per minute, the rate of flow appeared to increase progressively as the rate of compression was increased. This was true when the blood volume had been depleted and the heart felt relatively empty as well as when venous return was adequate and the heart felt full in the operator's hand.

Comparison of Blood Flow Due to Spontaneous Heartbeat and to Cardiac Massage.—In Table II the rate of blood flow in the thoracic aorta is shown with (a) spontaneous heartbeat with an open chest and (b) cardiac massage at 60

TABLE I. EFFECT OF THE RATE OF CARDIAC COMPRESSION ON BLOOD FLOW (CUBIC CENTIMETER PER MINUTE)

	EXPERIMENT	30 PER MIN.	60 PER MIN.	120 PER MIN.
Thoracic aorta	132		172.0	226.6
	138	109.6	193.2	250.5
	141	151.1	262.1	278.3
	142	202.3	324.6	408.6
	143		222.6	322.1
	145	83.6	143.1	212.64
Carotid artery	150	20.1	37.0	42.5
	149	16.9	31.5	43.8
	151	15.1	28.5	33.2

TABLE II. BLOOD FLOW DUE TO SPONTANEOUS HEARTBEAT AND CARDIAC COMPRESSION (CHEST OPEN, AORTA CANNULATED)

EXPERIMENT	SPONTANEOUS CARDIAC ACTIVITY (C.C. PER MIN.)	CARDIAC MASSAGE (C.C. PER MIN.)		B. P.
		60 PER MIN.	120 PER MIN.	
132	439.8	172.0	226.6	–
134	405.6	282.6		–
138	434.4	193.2	250.5	90
141	365.4	262.0	178.3	70
142	256.8	324.6	408.6	30
143	277.0	222.6	322.0	30
145	402.6	143.1	212.6	90

and 120 times per minute. In two instances (Experiments 142, 143) it was possible to move more blood by cardiac compression than was moved by the spontaneously beating heart. In both of these experiments the systolic pressure had dropped to 30 mm. Hg following cannulization of the aorta, and this undoubtedly accounted for the relatively slow rate of blood flow before the heart was stopped. In all other instances the rate of blood flow during cardiac massage was less than before the heart was stopped. In no instance, however, was the rate of flow due to cardiac compression at 120 per minute less than one-half of that resulting from the normal spontaneous heartbeat.

The Effect on the Carotid Circulation of Occlusion of the Thoracic Aorta During Cardiac Massage.—Since cerebral cortical tissue is believed to be the most sensitive to anoxic damage during cardiac arrest, it was of interest to determine whether cerebral blood flow could be increased by occlusion of the thoracic aorta during cardiac massage. Wiggers[9] suggested this maneuver to increase coronary artery flow, but, to our knowledge, it has not been used or studied as a procedure to increase cerebral blood flow and oxygenation during cardiac resuscitation. Table III shows the marked increase in carotid blood flow in three experiments.

TABLE III. EFFECT ON CAROTID BLOOD FLOW OF OCCLUSION OF THE THORACIC AORTA DURING CARDIAC MASSAGE

EXPERIMENT NUMBER	AORTA PATENT (C.C. PER MIN.)	AORTA OCCLUDED (C.C. PER MIN.)
136	31.2	54.5
150	26.4	55.1
159	27.0	51.7

It is evident that a considerably larger volume of blood was delivered to the cerebral tissues during cardiac compression when a noncrushing clamp was applied to the thoracic aorta.

The Effect of the Rapid Administration of Intravenous Fluids on the Rate of Blood During Cardiac Massage.—After fifteen to twenty minutes of cardiac massage the blood flow in the thoracic aorta and carotid artery decreased significantly in most experiments. When this occurred, the heart felt empty and there appeared to be inadequate diastolic filling. Although intravenous saline solution had been continuously administered at a moderate rate, oozing from the incision, due to heparinization, was rapid. The poor venous return to the heart appeared to be due to a decreased blood volume. When saline solution or blood was injected rapidly (50.0 c.c. per minute), the heart could be felt to fill in the operator's hand and the blood flow returned to, or exceeded, that obtained soon after the heart was stopped. In Experiment 132, for example, the blood flow through the thoracic aorta soon after the heart was stopped was 172 c.c. per minute. Ten minutes later, when the heart felt empty, the rate of flow had fallen to 81.6 c.c. per minute. After 600 c.c. of blood were rapidly given (150 c.c. per minute), the blood flow increased to 202.8 c.c. per minute.

Because of the generalized vascular and capillary dilatation which follows cardiac arrest and the low systolic pressure produced by cardiac compression (40 mm. Hg), the venous return to the heart is presumably poor during attempted cardiac resuscitation. The rapid intravenous administration of blood might increase the venous return sufficiently to provide an increased increment in the cardiac output of oxygenated blood to the brain and other vital organs. This was done in Experiment 134. Soon after the heart was stopped, before there had been a significant depletion of the blood volume, 500 c.c. of blood were given intravenously in three minutes. The rate of blood flow in the thoracic aorta increased from 282.6 to 344.6 c.c. per minute.

Other Observations.—In Experiment 157, in which the bubble meter was connected to the abdominal aorta retroperitoneally, three other points were studied, as follows:

1. Does artificial ventilation of the lungs with intermittent intratracheal positive pressure produce significant circulation of blood? Immediately after the heart was stopped an air bubble was introduced. It did not move. Any movement of blood which may result from artificial ventilation, as demonstrated by Thompson, Quimby, and Smith[10] with a radioactive tracer technique, was not apparent in the bubble meter.

2. Is cardiac massage through the intact diaphragm effective? An upper midline incision was made, and the operator attempted to compress the heart without dividing the diaphragm. The heart could not be grasped, but blood flow at a slow rate (17.0 c.c. per minute) resulted from rhythmic thrusts at a rate of 60 per minute against the apex of the heart.

3. Is compression of the heart against the anterior chest wall an effective method of cardiac massage? The chest was opened and this maneuver, at a rate of 60 per minute, resulted in a blood flow of 41.6 c.c. per minute which was about

one-half the rate of 76.0 c.c. per minute produced by holding the heart and compressing it between the fingers and thumb.

COMMENT

The use of the bubble meter, an accurate instrument for measuring blood flow, afforded an opportunity to study certain details of the technique of cardiac massage. The first attempts of all who tried the procedure were relatively ineffectual. Practice was required in order to obtain maximal rates of blood flow. There were several minor variations in the technique of holding the heart which were considered preferable by different observers, but the most effective maneuver appeared to be compression between one or more digits in front and one or more digits behind the heart. The human heart, in our experience, may be too large to hold effectively in one hand, and it may be preferable to apply compression between two hands. Compression of the dog's heart against the anterior chest wall was relatively unsuccessful, and massage through the intact diaphragm proved to be a poor method. Although some circulation has been shown by radioactive tracer techniques to result from artificial ventilation of the lungs,[10] it was not sufficient to be detectable with the bubble meter in our experiments.

The optimum rate at which the heart should be compressed appears to be the fastest rate at which the heart can be compressed—at least up to 120 per minute. At rates approaching 120 per minute, fatigue of the operator becomes a limiting factor. Whereas a rate of 60 per minute could be maintained for twenty-five to thirty minutes without great discomfort, a rate of 120 per minute could not be continued for more than a few minutes because of cramping pain in the forearm. In patients requiring cardiac massage for more than a few minutes it would seem advisable, therefore, to provide a substitute for the operator in order to maintain a rapid rate.

The increase in carotid blood flow which followed occlusion of the thoracic aorta during cardiac massage in dogs is regarded as evidence in favor of applying a noncrushing clamp or manual pressure, at least intermittently, to the thoracic aorta of patients during cardiac resuscitation. The additional oxygenation provided to the brain and myocardium[9] at the expense of some oxygen deprivation of the more resistant organs below the point of aortic occlusion is probably warranted during the brief period in which the issue of restoration of the heartbeat is settled.

The importance of maintaining an adequate blood volume and supporting the venous return to the heart by the rapid intravenous administration of blood or physiologic saline solution became evident in these experiments. In the excitement and confusion which may acompany attempts at cardiac resuscitation in patients, intravenous therapy must not be neglected.

CONCLUSIONS

1. The technique of cardiac massage was studied in dogs using the bubble meter of Dumke and Schmidt to measure the rate of blood flow.

2. The rate of blood flow in the carotid artery and thoracic aorta increased as the rate of cardiac compression was increased from 30 to 120 times per minute.

3. The rate of blood flow during cardiac massage was approximately one-half of that produced by the spontaneous heartbeat with an open chest.

4. Maximal rates of blood flow during cardiac massage could not be maintained without supporting the blood volume with liberal quantities of blood or physiologic saline solution.

5. The rate of blood flow in the carotid artery during cardiac massage was significantly increased by occlusion of the thoracic aorta.

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AN EVALUATION OF ELECTROGASTROGRAPHY IN THE DIAGNOSIS OF GASTRIC CANCER

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THE electrogastrogram, as performed in this series, is a chart on which the potential difference between the gastric mucosa and the skin is plotted against time for thirty minutes. After the first fifteen minutes the subject drinks 200 c.c. of whole milk. The clinical application of the measurement of gastric potential was made by Goodman[1] in 1942. The physiologic experiments on which it is based go back at least fifty-nine years to the work of Biederman,[2] Bohlen,[3] and others.

In this paper the method will be described first. It has been modified slightly from that of Goodman.[1] Next, the results in patients will be presented. The results have been analyzed in two ways; first, by comparing the interpretation of the electrogastrogram recorded preoperatively with the pathologic findings at operation, and, second, by setting up certain rigid, wholly objective criteria by which all records could be classified as (1) undiagnosable, (2) indicative of a benign status, and (3) indicative of malignancy. Finally, a few observations made to throw light on the relation of gastric potential to gastric hydrochloric acid secretion will be reported and the recent literature on this subject alluded to.

Fig. 1 shows the test in progress. The Levine tube to the stomach is filled with 0.1 N hydrochloric acid which permeates a sponge rubber plug in the lower end of the tube and, at the outer end, connects through a calomel half cell to a high resistance recording potentiometer. The lower end of the tube is placed under fluoroscopic control against the gastric wall opposite the esophageal opening. The other electrode is filled with 0.1 N sodium chloride and placed against a scarified area on the skin surface of the arm. If these two electrodes are brought into direct contact through a potassium chloride bridge, no potential results.

After the gastric tube is placed, the patient lies down. The leads are connected to the potentiometer and a record begun. The normal stomach is electrically negative to the skin by a potential difference of 20 to 80 millivolts. After a base line has been obtained, the subject drinks 200 c.c. of milk and the record is continued an additional fifteen minutes. The test should be run after a fast of at least twelve hours. Typical responses are shown in Fig. 2. The normal stomach has a smooth, even base line between 20 and 80 millivolts. The response to milk at the fifteen-minute mark is prompt and smooth, gradually rising and then falling to the previous base line. On the

Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 24-26, 1949.

occurrence of a gastric lesion, such as gastric ulcer, the base line becomes more uneven. The response to the ingestion of milk in benign lesions is, in most cases, immediate and prolonged. The response to milk may itself be very uneven.

In patients with duodenal ulcers with simultaneous gastric lesions, the curve tends to resemble the curve of a gastric ulcer. In patients with gastric carcinoma, the base line is moderately to extremely uneven; the response to milk becomes atypical in 87 per cent of the cases. The response either does not take place in less than sixty seconds, or never gets greater than 3 mv, or does not last as long as three minutes.

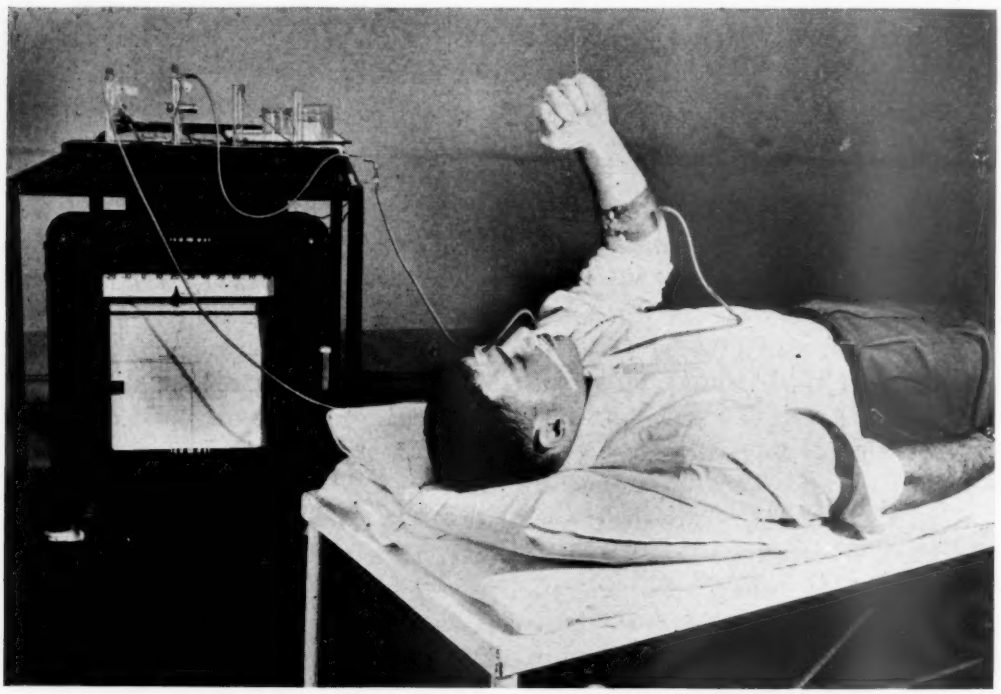

Fig. 1.—The technique of electrogastrography.

RESULTS

One hundred six patients were tested, 130 tests being run. Forty-two additional experiments were run on subjects presumed to be normal. In these, only twenty tests in twelve individuals were run with milk. All of these gave normal responses. Of the 106 patients, seventy-six were subsequently operated upon and a pathologic diagnosis obtained. The other thirty patients were not operated upon, but accumulated strong clinical evidence indicated that no malignant lesion of the stomach existed. So far there has been no reason to reverse the diagnosis in any of these thirty patients. Comparison of the immediate electrogastrographic diagnosis with the final diagnosis thus obtained showed that, of those subjects who had no malignancy, the test was interpreted as indicative of a benign status in sixty-two of seventy-one patients, or 87 per cent.

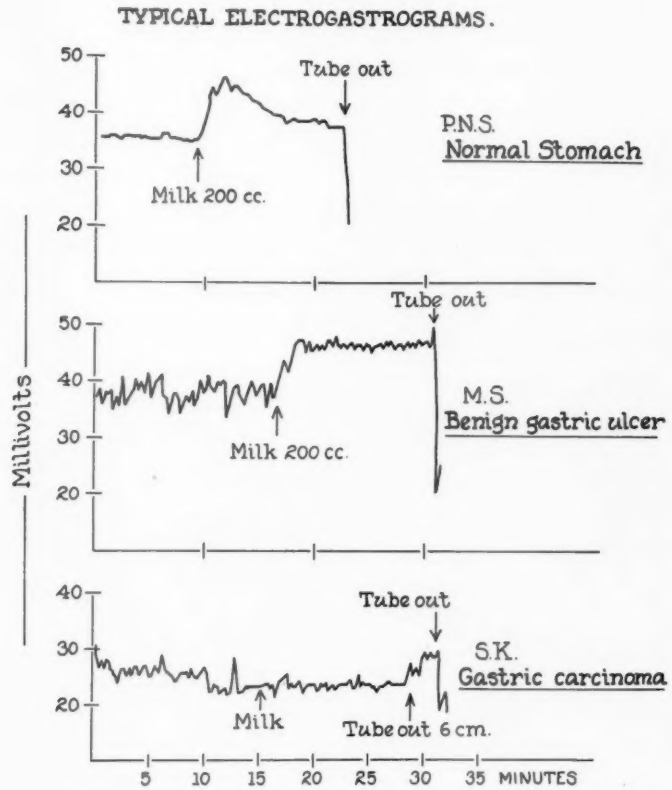

Fig. 2.—The records illustrate typical curves obtained from a subject with a normal stomach, a patient with gastric ulcer, and a patient with gastric carcinoma. The occurrence of gastric ulcer usually makes the base line more uneven, while the presence of gastric carcinoma dimishes the response to the milk meal in most instances.

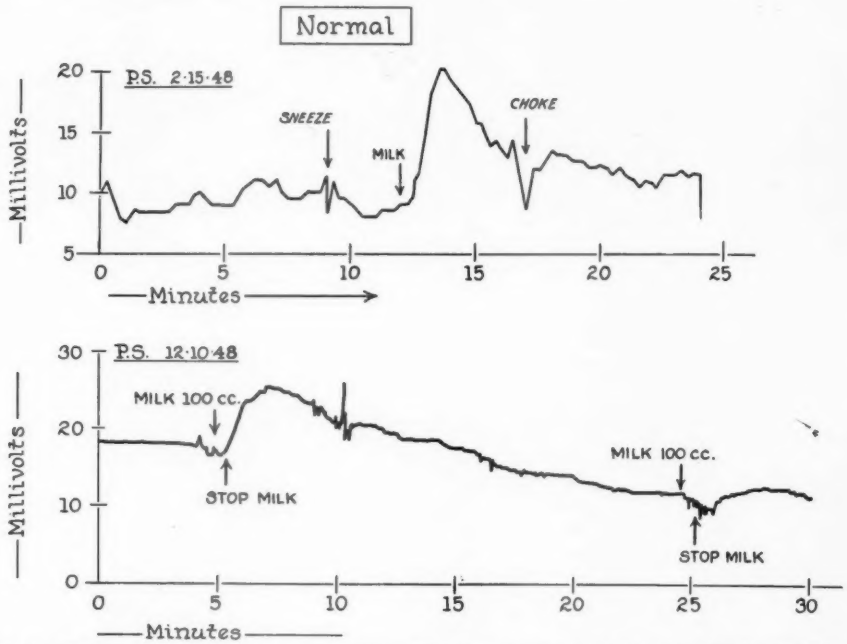

Fig. 3.—Two normal curves are shown. The top curve is a record obtained with a hand-operated potentiometer. The bottom record is from the same patient using the Speedomax Recorder (an automatic recording potentiometer, Leeds and Northrup Co., Philadelphia, Pa.)

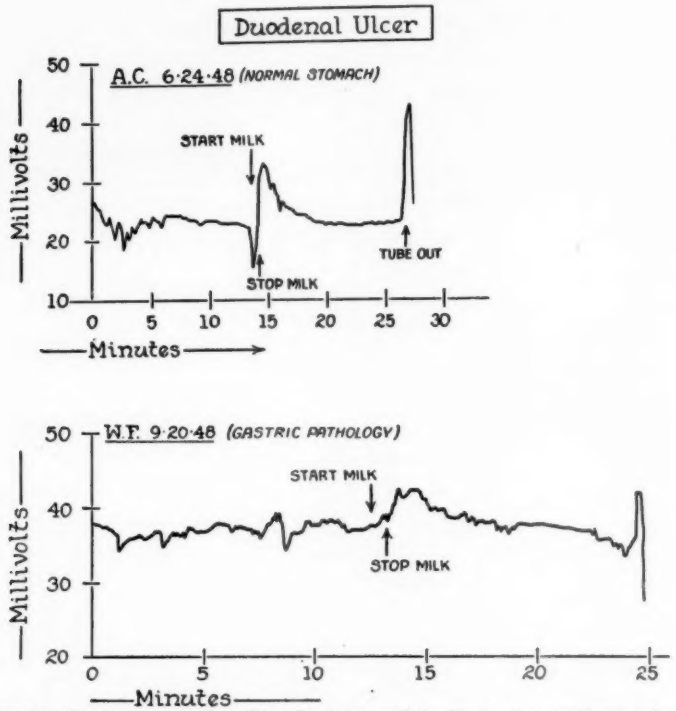

Fig. 4.—Duodenal ulcer records. The first record is that of a patient who had a duodenal ulcer with no concomitant gastric lesion. The base line is smooth. The response to milk is more spiking than that usually observed in a subject with a normal gastrointestinal tract. The second record is from a test on a patient who had a duodenal ulcer with concomitant gastritis. The base line is more uneven and tends to simulate that of gastric ulcer.

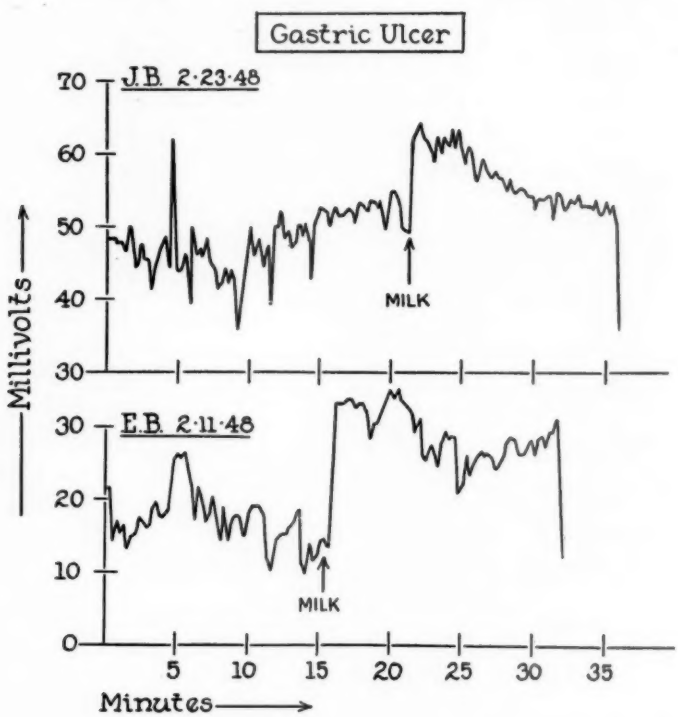

Fig. 5.—The presence of gastric ulcer often causes an extremely uneven base line. The response to milk is significant in the great majority of cases. The base line usually continues uneven after ingestion of milk.

In the thirty-five patients who proved to have gastric cancer, the test was interpreted preoperatively as indicating gastric malignancy in twenty-nine, or 83 per cent. Representative electrogastrograms are shown in Figs. 3 to 6. The normal subject has a smooth base line and a normal, smooth response to milk. The patients with duodenal ulcers have a smooth base line and a normal, but more striking, response to milk if there is no concomitant gastric lesion. With gastric disease, the base line tends to resemble that of gastric ulcer.

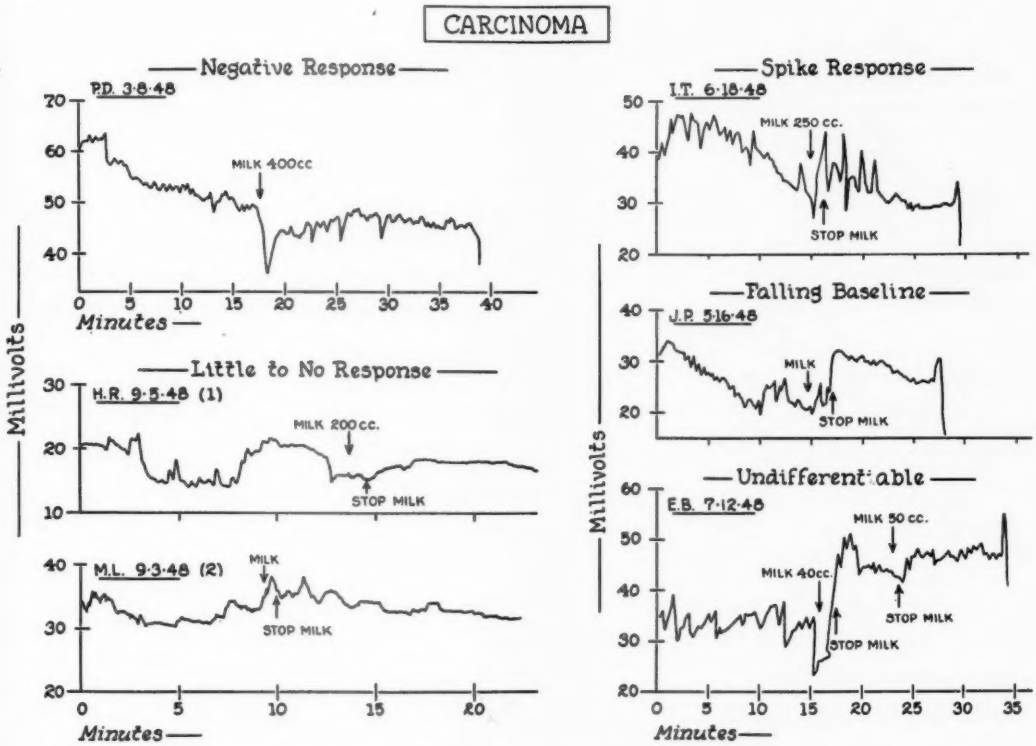

Fig. 6.—Six curves in patients with gastric carcinoma. All curves show a relative unevenness of the base line prior to the ingestion of milk. The responses to milk are divided into six types. Type 1 demonstrates a negative response to the ingestion of milk. Type 2 shows no response to milk. Type 3 illustrates a very slight response. The rise was no more than 3 mv and did not last longer than two minutes. Type 4 portrays a spikelike response to milk lasting less than two minutes. The fifth curve is one of a group which eventually was classified as undiagnosable. The falling base line is thought to be indicative of malignancy, but the response to milk is typical of a benign lesion. The sixth electrogastrogram shows the type of curve which is indistinguishable from those obtained in certain benign lesions.

Patients with gastric ulcers have an uneven base line of 18 to 60 mv with an uneven, but significant, response to milk, usually greater than in the case of the normal stomach.

The occurrence of gastric malignancy makes the base line very uneven, in general. The response to milk in the patient with gastric carcinoma (Fig. 6) has been divided into six groups.

Fearing that the appearance of the patient or chance information about other clinical findings might influence the interpretation of the less typical records, the records were later reviewed in accordance with the criteria shown in Table I.

TABLE I. AN OBJECTIVE METHOD FOR THE INTERPRETATION OF ELECTROGASTROGRAMS

Group I—Not interpretable	
	(a) Slope of base line changes more than 8 mv in 15 min.
Group II—Benign lesions	
	(a) Rise in potential of at least 3 mv
	(b) Rise must start within 1 min. of ingestion of milk and last at least 3 min. before potential returns to previous level
Group III—Malignant lesions	
	(a) All other curves

On this basis, it was necessary to discard nine tests, 8.5 per cent of the records, as uninterpretable. Of those remaining, the percentage of correct diagnoses in the thirty cases of gastric cancer with interpretable records was 87 per cent, and the percentage of correct diagnoses of the absence of gastric cancer in those sixty-seven with interpretable electrogastrograms was 88 per cent. While the series is not large, we believe that it is large enough to indicate that gastric cancer does usually alter the electrical response of the fasting human stomach to the ingestion of milk and to indicate that the relation is not invariably present and, hence, probably not a direct relationship but one which may perhaps be mediated through other changes which occur frequently but not constantly with gastric cancer.

Initially, we considered five possible ways in which the potential difference might be altered by the ingestion of milk.

1. Chemical reaction of the milk with the gastric contents
2. Chemical reaction of subsequent gastric secretions with the milk
3. Action currents due to muscular contractions in the stomach
4. Action currents due to muscular contractions elsewhere
5. Electrochemical changes in the cells associated with their secretory activity

Goodman[1] tested the first hypothesis by adding the milk to gastric juice in vitro. The typical changes did not occur. We have repeated this work and found that, while the measured potential will change on the addition of milk to gastric juice, it will in no way change as significantly as did the potential change in vivo. The curve type in vitro is not similar to that in vivo; the addition of milk changes the potential difference measured in a stepwise manner as would be expected if pH were increased in steps. The potential never returns to its previous level as it does in vivo. The variability in response in the human stomach would also tend to demonstrate that the potential is not simply a change in pH or diffusion potential.

There are several bits of evidence against the second hypothesis (that the changes are due to subsequent secretion into the milk meal). Several authors[4] have shown that hydrochloric acid is secreted at an almost constant concentration with a pH near 1.0. Hollander[4] and Lifson, Varco, and Visscher[5] have shown that the ionic concentration of gastric secretion is remarkably constant. Furthermore, we have observed that patients with achlorhydria may give a normal electrical response, which would be indicative evidence against both the first hypotheses.

As Tables II and III show, histamine hypodermically gives a fall in potential, and atropine, a rise in potential. The response to histamine might suggest that increased secretion of hydrochloric acid leads to a decrease in potential in an external circuit. Likewise, the response to atropine might suggest that a rise in potential accompanies the inhibition of gastric acid secretion by this drug. Thus, a rise in potential might indicate an inhibitory phenomenon.

TABLE II. ANALYSIS OF RESPONSE OF GASTRIC POTENTIAL TO ALCOHOL, HISTAMINE, ATROPINE (AND DERIVATIVES)

DRUG	METHOD ADMINISTERED	NUMBER OF TESTS	LEAST RESPONSE (MV.)	GREATEST RESPONSE (MV.)	MEAN RESPONSE (MV.)	LONGEST DURATION (HR.)	SHORTEST DURATION (MIN.)	MEAN DURATION (MIN.)
25% whiskey, 200 c.c.	P.O.	5	– 5*	–30	–19	1	15	27
Histamine, 0.3 mg.	S.C.	5	– 4	–13	– 9	1+	15	26
Atropine, 0.7-0.8 mg.	S.C.							
Dibutoline, 10.0 c.c.	S.C.	4	+23	+35	+24.75	1+	20+++	30†
(Atropine-like drug)								
Urecholine, 10.0 mg.	S.C.	1			– 9			30++

*Following previous ingestion of alcohol.
†Until could not stand intestinal contractions any longer.

TABLE III. THE RESPONSE OF GASTRIC POTENTIAL TO VARIOUS PHARMACOLOGIC AGENTS

TEST	SUBJECT	RESPONSE (MV.)	DURATION
25% alcohol, 200 c.c.	P. N. S.	– 5	15 min.
25% alcohol, 200 c.c.	P. N. S.	– 8	1 hr. +
25% whiskey, 200 c.c.	P. N. S.	–30	20 min. +
25% whiskey, 150 c.c.	R. P.	–25	17 min. +
25% alcohol, 200 c.c.	J. N.	–20	23 min. +
Histamine, 0.3 mg. (S.C.)	P. N. S.	– 4	15 min.
Histamine, 0.3 mg. (S.C.)	P. N. S.	– 6	60 min. +
Histamine, 0.4 mg. (S.C.)	P. N. S.	–12	15 min.
Histamine, 0.3 mg. (S.C.)	R. P.	–10	20 min.
Histamine, 0.3 mg. (S.C.)	J. N.	–13	20 min.
Atropine, 0.9 mg. (S.C.)	P. N. S.	+35	45 min. +
Atropine, 0.8 mg. (S.C.)	R. P.	+14	25 min. +
Atropine, 0.8 mg. (S.C.)	J. N.	+27	35 min. +
Dibutolene, 50.0 mg. (S.C.)	P. N. S.	+23	60 min. +
Urecholine, 10.0 mg. (S.C.)	P. N. S.	– 9	30 min. +

The third hypothesis, that the changes are due to action potentials associated with the contraction of the gastric muscles, is refuted by the fact that urecholine, which stimulates gastric contractions, did not increase the irregularity of the electrogastrogram. Furthermore, gastric potential is relatively constant in fasting normal stomachs until stimulated by milk, whereas gastric muscle action potentials are a periodic phenomenon. The same potential level is obtained in stomach mucosae from which the muscularis has been dissected away. (Rehm[6] and Sawyer and Rhoads.[7]) Davies and coworkers[8] were able to measure the same potential level in free, isolated frog gastric mucosa.

The theory that the action current of skeletal muscle produced the changes was refuted by moving the arm to which the skin electrode was attached and

by running in place. Neither of these activities materially affected the gastric potential as recorded.

By a process of exclusion, one is led toward the belief that the potential results from metabolic activity of the secretory cells. Rehm[6] brought forth evidence in the dog which we have confirmed, indicating that the potential arose in gastric mucosa from which all muscle layers had been removed except the muscularis mucosae, which cannot readily be separated. Fig. 7 shows the electrical responses of the human stomach to histamine, atropine, and ethanol. The effect of histamine on the human stomach is similar to that observed in the dog by Rehm[9] and in the isolated frog stomach by Crane, Davies, and Longmuir.[8, 10] This leads us to believe that we are measuring the same phenomenon.

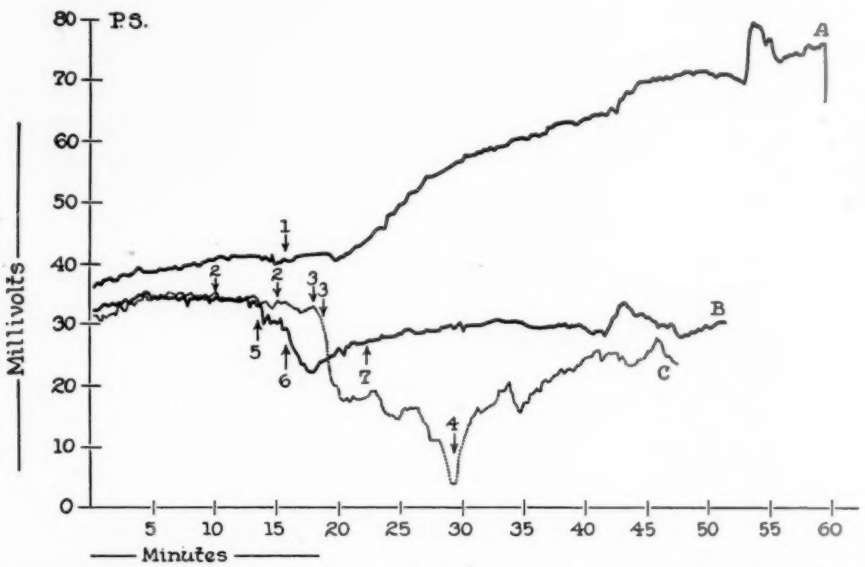

Fig. 7.—Superimposed graphs of the relative responses of gastric potential to histamine atropine, and alcohol on three successive days in the same normal subject (P. N. S.).

1, 0.9 mg. atropine admininstered subcutaneously; *2*, Smoking cigarette; *3*, 150 c.c whiskey and distilled water (25 per cent alcohol); *4*, 200 c.c. whole milk by mouth; *5*, Histamine, 0.4 c.c. 1/1000, subcutaneously; *6*, Effects of histamine noted subjectively—flushing, more rapid pulse, bitter taste; 7, Repeated sneezing.

The curves show the marked difference in effect of the three pharmacologic agents. The histamine test is similar to that obtained by Rehm[9] in the dog stomach and by Crane, Davies, and Longmuir[8, 10] in isolated frog gastric mucosa except that it is not quite as long in duration, perhaps due to the fact that only 0.4 c.c. of 1/1000 histamine was injected subcutaneously in a single dose.

All of these workers have tentatively shown that the energy necessary for the increased production of hydrochloric acid under histamine stimulation corresponds to the decrease in electrical energy in an external circuit which occurs with this drug. The latter authors showed that oxygen deprivation stopped hydrochloric acid secretion and reduced the potential to zero. Both could be restored by oxygenation. It is, therefore, postulated that the acid secreting oxyntic cells develop energy by combustion of foodstuffs which is evident as external electrical energy on the one hand, or utilized in formation of acid on the other. When secretion is stimulated by histamine, more

of this energy is utilized in the formation of hydrochloric acid which, it is postulated, takes place by the dissociation of H_2O into H^+ and OH^- ions in the oxyntic cells. As the secretion of hydrochloric acid occurs, less energy is available as external electrical energy. The reverse is true when atropine is used.

SUMMARY

A series of 150 electrogastrograms has been analyzed. Of these, 130 were run on 106 patients and twenty on twelve normal subjects. The method employed, which is a modification of that reported by Goodman, has been described. The origin of the gastric potential and its relation to gastric secretion have been considered in the light of certain experimental observations and in the light of recent reports in the physiologic literature. Two ways of analyzing the results in patients were employed. By the more objective of the two, 8.5 per cent of the records had to be discarded, but, in the remainder, the test was correct in 87 per cent of the patients with malignant gastric lesions and in 88 per cent of the patients who did not have malignant gastric lesions.

Thus, our experience confirms that of Goodman, and, while the test is not to be relied upon for definitive diagnosis of gastric malignancy, we believe it may prove of value as a screening test in cancer detection, for it should be less expensive than gastrointestinal x-ray examinations as now carried out.

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TOTAL GASTRECTOMY

Report of Sixty-Three Cases

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TWENTY-ONE total gastrectomies performed at the Johns Hopkins Hospital by one of us (W. P. L., Jr.) during the period of July, 1944, to December, 1945, were reported in a previous article.[1] Since that time, forty-two additional total gastric resections have been performed by the various members of the surgical staff of the Johns Hopkins Hospital. It is the purpose of this article to review the results obtained in this entire group of sixty-three cases, including the present status of the patients previously reported.

MATERIAL

The lesions treated by total gastrectomy in this group of sixty-three patients are listed in Table I. The indication for total resection of the stomach has been gastric malignancy in all cases but one, which was a case of gastroesophageal varices. This patient was a young man with Banti's syndrome and severe hematemesis, who had been subjected to many operative procedures before the introduction of lienorenal anastomosis. Subtotal esophagocardiectomy was ineffective. Total gastric resection has eliminated all signs of hemorrhage from the alimentary tract. In all the other cases the operator performed the resection in the belief that he was dealing with a malignant process. Three errors in the operator's judgment are indicated by the three patients with benign ulcer who were subjected to total gastrectomy. In one of the patients there was a large inflammatory mass around the ulcer; the other two had a large ulcer high on the lesser curvature.

The rationale of the total gastrectomy for malignant tumor of the stomach is to effect a block removal of the tumor and its primary avenues of invasion as radically as possible together with all regional lymph nodes. As Pack[2] has recently pointed out, this is the ideal operation for gastric cancer and is the only technique which embodies the reasoning which is followed in resections of mammary, colonic, and rectal carcinoma.

OPERATIVE TECHNIQUE

The technical procedure followed in these sixty-three cases has been fairly well standardized. The details of operative technique were presented in a previous communication.[1] An abdominal approach has been used in the majority of instances (Table II); usually an upper midline incision with extension up to the left of the xiphoid has been utilized. After determination of the operability of the tumor, removal of the stomach and the great omentum has been carried out in all cases. In no instance has this procedure been undertaken when

Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 24-26, 1949.

TABLE I. TOTAL GASTRECTOMIES (JULY 1, 1944, TO DEC. 31, 1948)

PATHOLOGIC LESIONS	NUMBER
Carcinoma of stomach	55
Leiomyosarcoma of stomach	1
Lymphosarcoma of stomach	1
Unclassified sarcoma of stomach	1
Syphilis of stomach	1
Gastroesophageal varices	1
Benign gastric ulcer	3
Total	63

TABLE II. OPERATIVE PROCEDURE IN SIXTY-THREE TOTAL GASTRECTOMIES

Operative Approach:		
Abdominal	57	
Thoracic	4	
Abdominothoracic	2	
Extent of Resection:		
Stomach and omentum		34
Stomach, omentum, spleen		16
Stomach, omentum, spleen, pancreas		5
Stomach, omentum, spleen, lower esophagus		3
Stomach, omentum, colon (transverse)		3
Stomach, omentum, colon (transverse), spleen		1
Stomach, omentum, left lobe of liver		1
Types of Anastomoses:		
Esophagojejunostomy (end-to-side)		57
with enteroenterostomy	24	
additional colonic anastomosis	4	
Esophagoduodenostomy		6

distant metastases were known to be present. In Table II the organs removed in this series in addition to the stomach and the omentum are shown. These resections were done because of direct extension of the tumor into adjacent viscera, excepting the spleen. The spleen was not removed routinely in this series, but splenectomy was done when the operator thought there was possibility of extension into the gastrosplenic ligament or when the splenic pedicle was damaged during the course of mobilization of the stomach. In the majority of instances, after resection of the stomach an anastomosis was carried out between the end of the esophagus and the side of the jejunum. There were fifty-seven such esophagojejunostomies. The loop of jejunum was usually brought up through a rent in the mesentery behind the transverse colon, but in several instances an antecolic type of anastomosis was carried out. An additional enteroenterostomy between the afferent and efferent limbs of the jejunal loop was performed in twenty-four instances. Six patients were treated by esophagoduodenostomy. The feasibility of this procedure, which was first demonstrated by Brigham[3] in 1898, depends on the mobility of the duodenum. The anastomoses between the esophagus and the intestine have been constructed with an outer row of interrupted sutures of medium silk and an inner row of closely placed interrupted sutures of fine catgut or of fine silk. Continuous sutures have been avoided in order to obviate subsequent stricture formation.

POSTOPERATIVE MANAGEMENT

During and immediately after operation 1,000 to 1,500 c.c. of blood have usually been given to these patients. Their postoperative management has be-

come fairly well standardized in that they are kept on parenteral feeding with nothing by mouth for a period of four days. On the fourth or fifth day they have been started on a graduated liquid diet beginning with 30 c.c. of water each hour, increased slowly with the patient's tolerance to a full liquid diet by the sixth or seventh day. The majority of patients have been able to take soft solid diet in six small feedings by the eighth to tenth day. Practically all of them have been discharged on a full soft diet in six small feedings. Supplemental vitamins and ferrous iron have usually been added to this dietary. Penicillin has been administered in full doses in all cases for the first postoperative week, after which it has usually been discontinued. In a few of the more recent cases streptomycin has been added to this prophylactic antibiotic therapy. In most instances, prior to discharge a postoperative fluoroscopy with barium has been carried out and also an endoscopic examination. No strictures at the line of anastomosis between esophagus and intestine have been encountered. The majority of patients have been discharged from the hospital by the fourteenth postoperative day.

OPERATIVE MORTALITY RATE AND POSTOPERATIVE COMPLICATIONS

There have been six deaths in the immediate postoperative period among these sixty-three cases of total gastrectomy, an operative mortality rate of 9.5 per cent. The causes of death are given in Table III. Frank leakage at the esophagojejunal suture line has been the cause of death in three instances. In two of these cases it was felt that dehiscence or necrosis at the suture line occurred because of interference with the blood supply of the lower esophagus, and in the other case leakage clearly resulted from necrosis of the jejunal wall at the stoma following an effort to construct a food pouch between the limbs of the jejunum.

The postoperative course of the majority of the fifty-seven individuals who survived operation has been quite uneventful. Thirty-seven of these patients had no significant difficulties. In Table IV the postoperative complications

TABLE III. POSTOPERATIVE DEATHS IN SIXTY-THREE TOTAL GASTRECTOMIES

PATIENT	OPERATION	SURVIVAL (DAYS)	CAUSE OF DEATH
J. J.	Total gastrectomy, splenectomy, partial colectomy, esophagojejunostomy, and colonic anastomosis	7	Leak at anastomosis (esophagojejunal)
E. W.	Total gastrectomy with esophagojejunostomy and long enteroenterostomy	10	Leak at anastomosis (esophagojejunal)
A. H.	Total gastrectomy, splenectomy with esophagojejunostomy	2	Pneumonia
L. W.	Total gastrectomy, splenectomy, partial pancreatectomy with esophagojejunostomy	15	Leak at anastomosis; pulmonary embolism
R. D.	Total gastrectomy, splenectomy with esophagojejunostomy	1	Coronary thrombosis
R. S.	Total gastrectomy with esophagojejunostomy	4	Afferent loop obstruction; uremia; bronchopneumonia
	Operative Mortality 9.5%		

TABLE IV. POSTOPERATIVE COMPLICATIONS IN SURVIVORS

Thromboembolism	5
Atelectasis	4
Subdiaphragmatic abscess	3
Pneumothorax	2
Pneumonia	2
Psychosis	2
Acute pancreatitis	1
Intestinal obstruction	1
Premature labor	1
Fecal fistula	1
Wound abscess	1

of a nonfatal nature are shown. There were no episodes of postoperative bleeding, no eviscerations, and no difficulties encountered with the duodenal stump.

Most of these patients have experienced varying degrees of epigastric fullness after being placed on solid food, but this has not been a particularly distressing symptom. About one-third of the survivors have had trouble with epigastric "burning" during and after meals. This symptom, which is apparently due to reflux of bile and pancreatic juice into the lower esophagus, has been transitory in most instances. It is encountered much less frequently in individuals who have had enteroenterostomy.

A comparison of the mortality rate of total gastrectomy for malignant gastric tumors with the operative mortality for partial gastric resection for such tumors at this clinic in the period covered by this study is given in Table V. This is a selected series in that it covers all the carcinomas and other malignant gastric tumors which have been explored in this hospital since the end of the previous study,[1] added to the twenty-five cases on which that report was based. One hundred forty-four individuals with histologically verified malignant gastric tumor were explored. In fifty-three of these cases the tumor was not resectable. In this group thirteen palliative gastroenterostomies were carried out. Ninety-one patients were treated by resection—a resectability rate of 63 per cent. The combined or over-all resection mortality rate was 13 per cent. The highest mortality rate was encountered in the cases of esophagocardiectomy and, interestingly enough, the operative mortality rate for total gastrectomy (10 per cent) is even less than the mortality rate for partial gastrectomy for gastric malignancy. These data are based on resections carried out for malignant tumors; the total gastrectomies which have been done for benign ulcer, syphilis, and varices are

TABLE V. SUMMARY OF SURGICAL EXPERIENCE WITH MALIGNANT GASTRIC TUMORS, JULY 1, 1944, TO DEC. 31, 1948

CASES	NUMBER	DEATHS	PER CENT MORTALITY
Explored	144	17	11
Not resectable	53	5	9
Gastroenterostomies	13	2	15
Resected	91	12	13
Total gastrectomies	58	6	10
Subtotal gastrectomies	23	3	13
Esophagocardiectomies	8	3	37
Local excision (malignant polyps)	2	0	0
Resectability Rate		63%	

not included in this group. There have been thirty-eight total gastrectomies for gastric cancer since the original report with four deaths, an operative mortality rate of 10.5 per cent in the more recent group. Although these data are based on too few cases to have any real statistical significance, nevertheless they indicate that total gastrectomy has become a reasonably safe surgical procedure.

PATHOLOGIC OBSERVATIONS

In twenty-five of the fifty-five total gastrectomies for carcinoma of the stomach and in the three resections for gastric sarcoma, the stomach was so extensively invaded by tumor that its gross removal would have been impossible by any resection less than total gastrectomy. In the remaining cases the tumor was fairly well localized either in the pyloric antrum or in the cardia so that its gross removal could have been accomplished either by high partial gastrectomy or by esophagocardiectomy. Unfortunately, a careful histopathologic study of the extent of the microscopic invasion of the gastric wall above and below the gross tumor has not been carried out in all cases. Coller, Kay, and MacIntyre[4] pointed out that in their experience the surgeon is likely to underestimate the actual margin of neoplasm in the wall of the stomach at operation in about 25 per cent of cases. Atkins[5] has recently described unpublished work in his department at Guy's Hospital in which careful histologic study of the upper margin of the line of resection in cases of subtotal gastrectomy for carcinoma has demonstrated the presence of malignant cells in eighteen of nineteen cases studied. Coller, Kay, and MacIntyre made a careful study of the regional lymphatic metastases of carcinoma of the stomach and found that it was impossible to tell without microscopic section whether the lymph nodes were invaded by metastases unless they were obviously completely replaced by carcinoma. In their cases they found metastases to the regional nodes in 75.5 per cent. In the fifty-five patients with carcinoma of the stomach treated by total gastrectomy in this group, 72 per cent had lymph node metastases. In Table VI we have divided these fifty-five cases of gastric carcinoma into Schindler's[6] modification of the Borrman[7] classification of gastric carcinoma, using the relatively loose terms "limited" and "infiltrative." Twenty-four of these cases fall into the group of "limited" carcinoma; thirty-one are considered to be "infiltrative." Of the twenty-four patients with "limited" carcinoma all but nine had metastases to the regional nodes, whereas in twenty-five of the thirty-one "infiltrative" carcinomas there were regional node metastases.

These data serve to emphasize the surgeon's lack of ability to judge accurately the extent of invasion of the gastric wall by the tumor and to recall the high incidence of invasion of lymph nodes even in apparently well-localized forms of gastric carcinoma.

TABLE VI. RELATION OF LYMPH NODE METASTASES TO GROSS TYPE OF TUMOR (SCHINDLER) IN FIFTY-FIVE CASES OF GASTRIC CARCINOMA

TYPE OF CARCINOMA	NODES NEGATIVE	NODES POSITIVE	PER CENT POSITIVE NODES
"Limited"	9	15	62
"Infiltrative"	6	25	80
Total	15	40	72

FOLLOW-UP STUDIES

In Fig. 1 the present status of the sixty-three patients treated by total gastrectomy in this series is summarized. Twenty-eight of these (44 per cent) are living today. Eighteen, or 29 per cent, of the group have lived for one year or more. Eleven of these eighteen are now alive one or more years after operation (18 per cent). Three patients are living more than four years after total resection of the stomach.

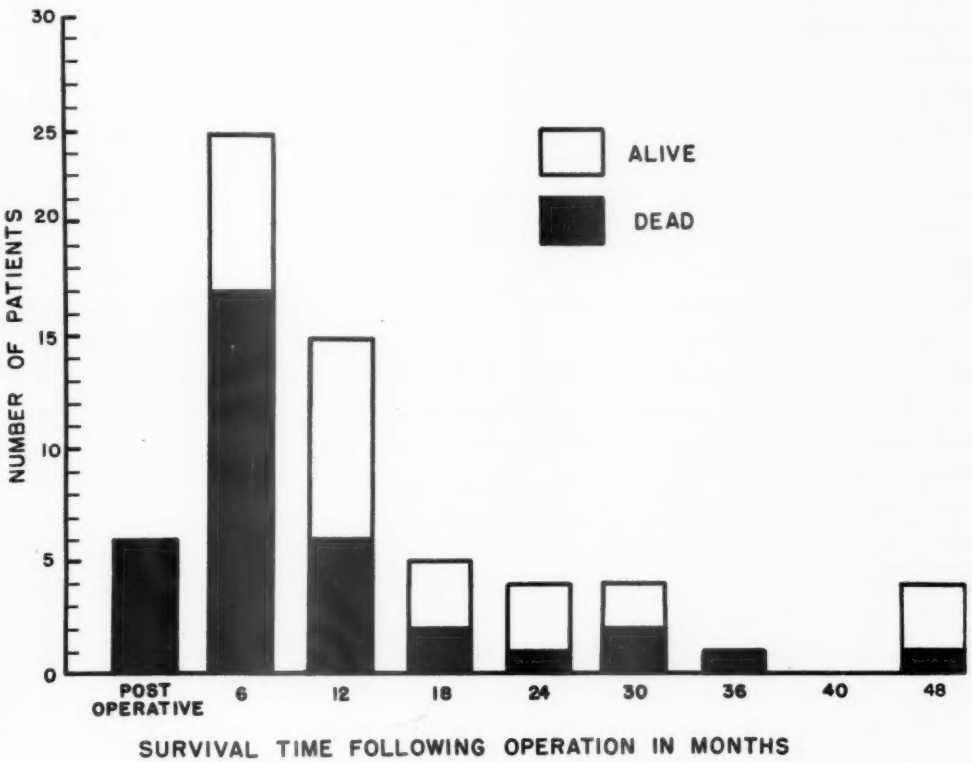

Fig. 1.—Present status of 62 patients treated by total gastrectomy; J. H. H. series, July 1, 1944, to Dec. 31, 1948.

Aside from the six postoperative deaths, seventeen patients have died in less than six months after total gastrectomy. It seems obvious in this group, by far the majority of whom have died with recurrent carcinoma, that total gastrectomy served only as a palliative procedure. All but two of these seventeen patients had extensive tumors with metastases to regional nodes at the time of operation. Biopsy of the tumor was carried out at the time of operation in fifteen cases. The majority of these individuals, who died in the first six months after operation, would fall into the group representing neglected cases in which the patients first appeared for definitive treatment twelve months or more after the appearance of symptoms of gastric disorder. In most of these cases the tumor was doubtless microscopically far beyond the limits of any possible block excision at the time of operation. It is also possible, however, that in a few instances the surgeon was guilty of seeding the peritoneum with carcinoma cells by poor technique in taking a biopsy of the tumor prior to resection or by ill-

advised manipulation of a tumor which had extended through to the serosal surface of the stomach wall.

A majority of these patients after discharge from the hospital have been followed by Paulson[8] in the gastrointestinal clinic of this hospital. The dietary regimen which he has worked out for them consists primarily of a high caloric, high protein, relatively low fat diet in five or six small, even feedings daily with supplemental vitamins, ferrous iron, and some form of protein hydrolysate. Paulson and his associates have made careful studies of the blood, stools, liver function, weight, appetite, food capacity, and dietary idiosyncrasies of these patients. Repeated endoscopic examinations have been carried out at intervals, and in no instance has any benign stricture of the esophagojejunal or esophagoduodenal junction occurred. In several patients dying of recurrence, a malignant obstruction has been demonstrated. In general it seems proper to say that fairly satisfactory biologic adjustment to the loss of the stomach has been made by the majority of individuals exclusive of those who have gone rapidly downhill with recurrent carcinoma. A majority of patients have gained weight after the operation, but as previously observed[1] very few of them have made a gain equal to the weight loss prior to operation. The food capacity of practically all the patients has been somewhat limited, and epigastric fullness after meals is a common complaint. Only seven individuals seem to have regained a truly normal food capacity. This fact probably is the explanation for the failure to regain normal weight. Diarrhea has not been a problem. A few patients have had transitory diarrhea in the immediate postoperative period, but none has had lasting difficulties of this type.

Postoperative symptoms of the so-called "dumping" syndrome or, perhaps better, the "intestinal distention" syndrome have been encountered in five individuals. This symptom complex has been transitory in most instances, however, and has not persisted after the first six months.

Epigastric and substernal distress of a "burning" type occurring a few minutes after meals has caused considerable difficulty for twenty-six patients. This symptom is almost certainly due to the regurgitation of bile and pancreatic juice into the lower esophagus. It has been encountered infrequently in patients with an enteroenterostomy placed below the esophagojejunal anastomosis. In most instances it has responded fairly satisfactorily to the administration of amphojel and has usually proved to be a transitory symptom persisting for only a few months after operation.

In Table VII we have summarized the pertinent data on eleven individuals who are alive today, twelve months or more after total gastrectomy. The longest survival time in this series is fifty-four months. All but three patients have made a fairly satisfactory gain in weight. The majority have a good appetite, and six of the twelve seem to have a normal food capacity. The remainder are still eating four to six small meals a day and do have a limited capacity. Only two of the eleven patients have no gastrointestinal symptoms either during or after meals. The majority complain of some degree of epigastric fullness and discomfort with or without associated heartburn at the time of or shortly after meals. All of these patients have normal bowel habits, and none of them are

TABLE VII. PATIENTS NOW ALIVE SURVIVING TOTAL GASTRECTOMY FOR ONE YEAR OR MORE

PATIENT	SURVIVAL TIME (MO.)	APPETITE	FOOD CAPACITY	G. I. SYMPTOMS	STOOLS	WEIGHT	ANEMIA	WORK	RECURRENCE
1. J. W.	54	Good	Normal	None	Normal	15 lb. gain	No	Regular	No
2. J. C.	52	Fair	4-5 meals per day	Fullness p. c.	Normal	20 lb. loss	No	Light	Benign ulcer
3. J. P.	49	Good	5 meals per day	"Heartburn" p. c.	Normal	13 lb. gain	No	Regular	No
4. L. S.	29	Good	Normal	None	Normal	5 lb. gain	—	Regular	Benign ulcer
5. J. H.	26	Good	Normal	None	Normal	10 lb. gain	No	Regular	No
6. H. F.	22	Fair	6 meals per day	"Heartburn" p. c.	Normal	Same	No	Regular	No
7. J. W.	21	Good	Normal	None	Normal	30 lb. gain	No	Regular	No
8. N. S.	19	Good	Normal	"Heartburn" p. c.	Normal	25 lb. gain	No	Regular	No
9. B. M.	16	Poor	6 meals per day	Much "gas" p. c.	Normal	35 lb. loss	No	None	?
10. F. B.	14	Fair	6 meals per day	Fullness p. c.	Normal	20 lb. loss	No	Light	?
11. W. C.	14	Good	Normal	Fullness p. c.	Normal	15 lb. gain	No	Regular	No

troubled with diarrhea, although it has been shown previously that because of the incomplete absorption of fats the stool may consist of 20 to 50 per cent of fats.

Blood studies have been carried out on all of these patients quite recently with one exception, and in no instance is there anemia. Only one patient shows a slight degree of macrocytosis by smear, but her blood indices are within normal limits. A majority of patients are working regularly and have been able to return to their usual occupations. One of these patients is doing heavy labor on a farm. Only two patients are unable to do full-time work, and in each instance recurrence of carcinoma is suspected.

DISCUSSION

In selecting an operation for the cure of malignant disease one must consider three factors: First, the operative mortality rate or the immediate danger of the operation; second, the adequacy of the procedure as a means of eradicating the tumor; third, the compatibility of the end result with continued health of the individual.

Total gastrectomy has now become a relatively safe procedure. In the present series of sixty-three cases, the mortality rate was 9.5 per cent. Forty-two of these operations were performed by men during the tenure of their surgical residency. As there has been only one death in the last thirty consecutive cases of total gastrectomy in the hospital, the operative mortality for this procedure has been only 3.3 per cent in the last two years of this study. Three of the six deaths in this series of sixty-three total gastrectomies are attributable to leakage at the esophagojejunal anastomosis. Esophagojejunostomy is obviously the most dangerous part of the procedure as regards the immediate postoperative course. We have had no experience in this group of patients with the Roux en-y type of anastomosis or with the type of esophagojejunostomy described by Roscoe Graham,[9] in which the anastomosis is buried by suturing the proximal and distal jejunal limbs around it. The end-to-side type of esophagojejunostomy as done in this series must be carried out with meticulous care in order to be successful. To summarize again the points in this regard: Too extensive mobilization of the esophagus out of the mediastinum is to be avoided because of the danger of impairment of its blood supply and because of the advantage of preserving the layer of fibrous areolar tissue which surrounds the abdominal esophagus. If the jejunal loop is short, tension may be avoided by dividing one or more vessels in the base of the mesentery. Interrupted sutures are used throughout in the anastomosis, and the internal layer is based on the approximation of the full thickness of the esophageal wall to that of the jejunum with closely placed interrupted inverted sutures with the knots tied on the inside of the lumen. Last, the anastomosis is supported by approximating a flap of peritoneum which is elevated from the abdominal esophagus and adjacent diaphragm down to the jejunum below the line of suture. It is our opinion at present that a long enteroenterostomy between the afferent and efferent jejunal limbs is advisable in order to obviate the postoperative "burning" syndrome.

Pack[2] recently described total gastrectomy as being the ideal operation for gastric cancer. To quote from his article, "If an organ is unessential for life the growing concept of cancer therapy more and more suggests sacrifice of the entire organ, the regional lymph nodes, and the intervening lymphatics." The block resection in total gastrectomy for cancer includes the entire great omentum, the proximal two centimeters of duodenum, the entire stomach, the entire gastrohepatic omentum, the spleen, and the lower two centimeters of the abdominal esophagus. Included in this block are the lymphatics and nodes along the greater curvature of the stomach, the nodes of the lesser curvature, the infrapyloric, retropyloric, and right gastroepiploic nodes, the nodes of the lienogastric ligament, the juxtacardiac nodes, and the nodes along the left gastric vessels and around the celiac axis. The peritoneum of the lesser bursa should be removed for any posterior lesion. If there is extension of the tumor into an adjacent organ (for example, transverse mesocolon, colon, left lobe of liver, tail of pancreas), such organs should be included in the block resection. Tumors of the cardia of the stomach involving the lower esophagus are best dealt with, in our opinion, by an abdominothoracic exposure which permits removal of the diaphragm adjacent to the tumor in addition to the entire stomach and the lower esophagus.

The chance for more complete removal of gastric carcinoma and its primary node metastases seems to us to be far greater by total gastrectomy than by partial gastrectomy. The argument that recurrence or death from carcinoma after partial gastrectomy usually is due to metastases rather than recurrence in the gastric stump has been used to question the necessity for total gastrectomy. One wonders if the more adequate removal of the lymphatic drainage areas of the stomach which is made possible by total gastrectomy will negate this argument. We have already pointed out the difficulties of the gross evaluation of the extent of a tumor in the wall of the stomach and have emphasized the high incidence (62 to 80 per cent) of lymph node metastases with gastric carcinoma regardless of whether the individual tumor is "limited" or "infiltrative." These factors certainly militate against the complete eradication of gastric carcinoma by subtotal gastrectomy. Our series of total gastrectomies for gastric carcinoma is too small and covers too short a period of time to permit any statistical comparison with late results obtained by subtotal gastrectomy. It may be pointed out, however, that three patients with gastric carcinoma treated by total gastrectomy in the earlier series survived without evidence of recurrence for four years or more after operation, and none of these patients had a lesion at the time of operation which could have been even grossly removed by partial gastrectomy.

The data presented in Table VII are submitted as evidence that a healthy life is possible after total resection of the stomach. The majority of patients in this series who are now alive after surviving total gastrectomy for one year or more are working regularly, have made a fairly good gain in weight since operation, and are leading a normal life with some dietary restrictions and some difficulties of a relatively insignificant nature related to fullness and distress after eating.

In the sixty-three total gastrectomies in this series, three errors in diagnosis resulted in three total gastrectomies for benign ulcer. One of these errors, occurring early in the series, prompted us to feel that a specimen for biopsy of the carcinoma or of the mass in the stomach should be taken before total gastrectomy is carried out. In the usual case of gastric cancer the diagnosis is obvious, and biopsy may be unnecessary; however, in less advanced cases and particularly when the surgeon is faced with the problem of a large gastric ulcer, biopsy is definitely indicated. It is our opinion that great care should be exercised in biopsy of a gastric cancer because of the danger of seeding the peritoneal cavity with cacinoma cells. Improper technique in biopsy of gastric carcinoma as has been followed in many of the cases of this series may be responsible for some of the deaths from recurrent carcinoma in the first six months after operation. A specimen for biopsy should be taken with the same precautions that are used in biopsy of a carcinoma of the breast. This is best done by placing a gastrotomy incision with the cautery through the stomach wall in a seemingly uninvolved quadrant and taking a segment of the suspected tumor from within the lumen of the stomach. The gastrotomy incision may then be closed by an uncontaminated assistant while the operator changes gloves and gown and discards the instruments used in taking the specimen. This precaution may eliminate or reduce contamination of the peritoneum with malignant cells.

CONCLUSIONS

Sixty-three total gastric resections are reported with a mortality rate of 9.5 per cent.

The majority of patients who survive operation without evidence of recurrence for six months or longer adjust themselves to a normal mode of living.

At present, survival times are too short and the number of cases of total gastrectomy too small to compare the late results with those following subtotal resection. There are, however, theoretical considerations and some actual indications from a series such as is herein presented that total gastrectomy is a more effective treatment of gastric cancer than is subtotal resection.

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OPERATIVE MANAGEMENT OF CARCINOMA OF THE COLON

Is Proximal Drainage of the Unobstructed Colon Necessary?

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THERE is no unanimity of opinion on what is the best operative procedure for carcinoma of the colon without obstruction. The surgeon may elect one of four methods: (1) primary resection and anastomosis without preliminary or concomitant proximal colostomy, (2) resection and anastomosis with proximal colostomy, (3) multiple stage procedures in which anastomosis precedes resection, and (4) the Mikulicz operation.

There is general agreement that if intestinal obstruction is present drainage by cecostomy or colostomy should precede resection.

The majority of surgeons provide drainage of the bowel proximal to the resection when little or no obstruction exists. This is not our policy. It is the practice of both the resident and senior surgeons of this clinic to do resection and primary anastomosis without preliminary or concomitant proximal drainage whenever it is possible. This method is not prescribed as obligatory and the surgeon is free to choose the procedure which in his judgment best meets the indications of the case. Thus, our elimination of proximal drainage in the unobstructed patient results from the conviction that it is not necessary. This view is contrary to the impression gained from the literature and from conversations with other surgeons. It appeared desirable to evaluate and compare our results with those of others in order to determine whether or not we were justified in our opinion. A study covering the last two decades is necessary, for the recent improvements in preoperative and postoperative care have made a profound change in the outlook. Technical proficiency has remained about the same.

This study evaluates the immediate results from resection of carcinoma of the colon (exclusive of the rectum) at the Strong Memorial Hospital from 1928 through 1947.

HISTORICAL BACKGROUND

Allen[1] in 1937 recommended for carcinoma of the right colon preliminary ileotransverse colostomy and secondary resection. In 1939, Allen and Welch[2] recommended for all cases of carcinoma of the colon a two-stage procedure with prior or complementary proximal decompression of the bowel. In 1943 Allen[3] reported an over-all mortality of 18 per cent in 186 cases. At that time he recommended preliminary ileotransverse colostomy and aseptic anastomosis for surgery of the right and proximal one-third of the transverse colon. He advocated preliminary tube cecostomy in dealing with cancer of the remaining portion of the colon. Allen, Welch, and Donaldson[4] in 1947 reported upon 105

Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 24-26, 1949.

patients operated upon since 1943. The over-all mortality in this group was 2 per cent. Allen[5] in 1947 stated that he believed in resection and primary anastomosis, and had come to believe that the open type of anastomosis was to be preferred to the closed type. He recommended cecostomy only in cases with acute, complete obstruction of the left colon and stated that concomitant cecostomy was rarely employed.

Many surgeons employ the "obstructive resection" described by Rankin. In 1930 Rankin[6] reported thirty-one operations done in this manner with only one death. At that time he pointed out that the operation should never be done in the presence of obstruction—a point which is frequently not appreciated.

In 1941 Rankin[7] referred to a gross mortality rate of from 6 to 10 per cent as a favorable one and one which any surgical procedure should be expected to achieve. At that time he advised the aseptic type of anastomosis, if anastomosis was to be done, although still advocating the obstructive type of resection. In regard to preliminary proximal drainage of the bowel Rankin[7] said, "One may not easily overemphasize the advantage of a complementary decompressing measure in the event one selects a single stage resection in either the right or left colon."

Cattell[8] in 1943 reported 133 cases of modified Mikulicz resections of the colon. In these cases there were fifteen deaths, a gross mortality of 11.3 per cent. In 1941 thirty-three operations were done with one death, representing a 2.7 per cent mortality. Cattell believed this modified Mikulicz procedure to be the operation of choice in carcinoma of the colon.

In 1932 Lahey[9] recommended that a modified Mikulicz type of procedure be done on the right colon, and in 1942 Lahey and Sanderson[10] reported 112 operations done in this manner.

In 1947 Mayo[11] stated, "For the past several years we have been performing a one stage right hemicolectomy for the right portion of the colon with an end to end open type of anastomosis between the terminal portion of the ileum and the transverse colon."

Cheever[12] in 1931 reported 154 patients with carcinoma of the colon operated on at the Peter Bent Brigham Hospital from 1913 to 1931. Eighty-five of these operations were radical resections; there were fifteen deaths, a mortality rate of 17.6 per cent. He found that when cecostomy was used an 8.5 per cent mortality resulted, and that without cecostomy the mortality rate was 24 per cent. He recommended resection and anastomosis in dealing with carcinoma of the colon, feeling that the Mikulicz type of procedure should be reserved for those cases with particular indications. He stated, "A general principle so widely accepted that it needs no support is that of the expediency of a preliminary proximal drainage operation."

Wangensteen[13] discussed aseptic resections of the gastrointestinal tract, and reported 100 consecutive cases handled by himself in seven months from March, 1940. In this group were fourteen colon resections with one death. Wangensteen[14] reported forty-six resections of the colon for carcinoma from 1941 to 1943; there was a mortality rate in this group of 2.1 per cent. At that

time Wangensteen advocated an aseptic type of anastomosis, and felt that preliminary proximal drainage of the bowel was not necessary.

Stone and McLanahan[15] in 1942 reported 104 cases of resection and immediate anastomosis. They had eleven deaths, a mortality rate of 10.6 per cent. They did preliminary cecostomy in only nine cases and did not think it necessary in nonobstructed cases.

Zinninger and Hoxworth[16] in 1943 reported forty-five cases of one-stage resection and anastomosis done from 1937 to 1943. In the absence of obstruction they did not carry out proximal drainage of the bowel. Their mortality rate was 8.8 per cent.

Whipple[17] reported his results in resection and anastomosis from 1933 to 1942. There were 111 resections of the left colon with a mortality rate of 12.6 per cent; 95 ileocolectomies were done with a mortality of 15.8 per cent; 23 resections of the transverse colon carried a mortality rate of 21 per cent.

McNealy and Lands[18] reported thirty-four cases of resection and anastomosis with two deaths. In this series were seven patients with obstruction, all treated conservatively. These authors stated, "The shortened hospital stay, the elimination of multiple operations, the savings in time, expense, and psychologic trauma together with a low mortality . . . make the procedure of resection with primary open anastomosis one of choice."

MacFee[19] stated, "Primary one stage resection and anastomosis may succeed in any part of the colon proper, but it should not be performed for tumors in the rectosigmoid and its use elsewhere should be limited to uncomplicated lesions."

PRESENTATION OF CASES

From 1928 through 1947, inclusive, 287 patients with carcinoma of the colon (exclusive of rectum) have been operated on. This series does not include patients who have had merely exploratory laparotomy without definitive surgery. It does not include patients who have had colostomy as a palliative procedure. Table I shows the various types of operative procedures which have been carried out. These 287 patients have been operated on by many different surgeons, both resident and attending.

In the first decade of the period studied (1928 through 1937), 74 patients were operated upon. In the second decade 213 patients were operated upon.

TABLE I. TYPE OF OPERATION DONE IN 287 CASES, 1928 TO 1947

OPERATION	1928 TO 1937	1938 TO 1947	TOTAL
Ileocolostomy with resection	20	66	86
Colocolostomy with resection	23	128	151
Ileocolostomy, delayed resection	8	5	13
Colocolostomy, delayed resection	1	1	2
Palliative ileocolostomy (no resection)	3	4	7
Palliative colocolostomy (no resection)	4	1	5
Mikulicz type of operation	15	8	23
Total	74	213	287

In each case material for pathological examination was obtained and the diagnosis of carcinoma confirmed by microscopic examination. There were 150 patients with carcinoma of the left colon, 39 with carcinoma of the transverse colon, and 98 with carcinoma of the right colon.

In Table I it can be seen that in only 23 instances was a Mikulicz procedure or one of its modifications carried out. Of the remaining 264 cases, 106 patients had an operation which involved an ileocolostomy and 158 had a procedure which involved colocolostomy.

MORTALITY

Of the twenty-three patients who had one of the Mikulicz procedures, there were six hospital deaths, a gross mortality of 26 per cent. The Mikulicz procedure has been reserved for cases with special indications—frequently poor-risk patients and those with obstruction. It has not been popular because of the high morbidity rate, the prolonged hospitalization, and the feeling that a radical resection cannot be carried out in this manner. If more favorable cases were treated by this method the resultant mortality would probably be appreciably lower.

In operations involving a bowel anastomosis, the gross over-all mortality for the twenty-year period has been 11 per cent. The mortality for the years 1928 to 1937 during which time 59 cases were done was 27 per cent. The mortality for the years 1938 to 1947 when 205 cases were done was 6.3 per cent. These figures are shown in Table II.

TABLE II. GROSS MORTALITY IN 287 CASES

OPERATION	CASES	DEATHS	PERCENTAGE
Mikulicz type of operation	23	6	26
Operation involving anastomosis			
1928-1937	59	16	27
1938-1947	205	13	6.3
Total	264	29	11

One sometimes hears the comment that resident surgeons should not do large bowel surgery because of the resultant high mortality. We agree completely that inexperienced surgeons in training should have close supervision when doing this type of work. The policy of this hospital is to supervise the resident surgeon until he attains sufficient proficiency to justify his assuming complete operative responsibility. This policy does not result in an increased mortality rate, as shown in Table III. During the second ten-year period, resident surgeons have operated on 76 patients with carcinoma of the colon and done anastomosis in each; there have been 5 hospital deaths, a percentage of 6.6 per cent. During the same ten-year period the attending surgeons have operated in 129 cases; there have been 8 hospital deaths, a mortality rate of 6.2 per cent.

TABLE III. COMPARISON OF MORTALITY FOR ATTENDING SURGEONS AND RESIDENT SURGEONS IN ANASTOMOSIS OF COLON

	RESIDENT			ATTENDING		
	CASES	DEATHS	PERCENTAGE	CASES	DEATHS	PERCENTAGE
1928-1937	6	1	16	53	15	28
1938-1947	76	5	6.6	129	8	6.2

Many surgeons feel that surgery of the left colon is attended by a higher mortality rate than surgery of the right colon. This has not been true in our series. As shown in Table IV, 106 patients have had ileocolostomy, with 15 hospital deaths, a rate of 14 per cent; 158 patients have had colocolostomy, with 14 hospital deaths, a rate of 8.9 per cent.

TABLE IV. MORTALITY, ILEOCOLOSTOMY VERSUS COLOCOLOSTOMY

	ILEOCOLOSTOMY			COLOCOLOSTOMY		
	CASES	DEATHS	PERCENTAGE	CASES	DEATHS	PERCENTAGE
1928-1937	31	9	29	28	7	25
1938-1947	75	6	8	130	7	5.4
Total	106	15	14	158	14	8.9

We have not attempted to break down the deaths into "medical" or "surgical" causes, or to separate the deaths directly due to surgery and indirectly due to surgery. Any patient who fails to leave the hospital alive, from whatever cause, after the operation is classified as a hospital death. Table V shows the proximate cause of death in the 29 cases out of 264. It is to be especially noted that the number of deaths from peritonitis and the number of deaths from surgical shock has been fewer in the second ten-year period, although more cases have been done in the latter decade.

TABLE V. CAUSES OF DEATH (29 CASES)

	1928 TO 1937	1938 TO 1947	TOTAL
Peritonitis	7	4	11
Surgical shock	4	1	5
Cardiac failure	2	2	4
Pneumonia	2	2	4
Pulmonary embolus	1	2	3
Cerebral hemorrhage	0	1	1
Inanition and senility	0	1	1
			29

Preliminary or concomitant proximal decompression of the bowel has been carried out only in those patients with demonstrable large bowel obstruction. It has not been used in cases with no obstruction. Table VI shows the comparative mortality for those cases in which proximal decompression was done and for those in which it was not done. In the second decade 42 operations involving bowel anastomosis have been done with proximal drainage. In this group there have been 2 deaths, a mortality rate of 4.7 per cent. During the same period of time 163 operations involving bowel anastomosis have been done without proximal drainage. In this group there have been 11 deaths, a mortality rate of 6.7 per cent.

TABLE VI. RELATION OF PROXIMAL DRAINAGE OF THE BOWEL TO MORTALITY

	PROXIMAL DRAINAGE			NO PROXIMAL DRAINAGE		
	CASES	DEATHS	RATE (PER CENT)	CASES	DEATHS	RATE (PER CENT)
1928 to 1937	19	2	10	40	14	35
1938 to 1947	42	2	4.7	163	11	6.7

MORBIDITY

We have compared the morbidity rate for ileocolostomy and for colocolostomy. All postoperative complications, however minor, are tabulated. Again, no attempt has been made to separate complications directly and indirectly due to operative technique. Furthermore, any patient remaining in the hospital longer than 21 days, even though a specific complication has not been observed, is classified as a complicated case. The average duration of the postoperative stay in uncomplicated cases has been 15.4 days.

The morbidity rate for ileocolostomy and for colocolostomy for the two ten-year periods has been compared. This is shown in Table VIII. Of 106 cases involving ileocolostomy, there have been 33 complicated cases, a rate of 31 per cent. Of 158 cases involving colocolostomy, 53 cases have been complicated, a rate of 34 per cent.

TABLE VII. MORBIDITY, ILEOCOLOSTOMY VERSUS COLOCOLOSTOMY

	1928 TO 1937			1938 TO 1947			TOTAL		
	CASES	COMPLICATIONS	PER CENT	CASES	COMPLICATIONS	PER CENT	CASES	COMPLICATIONS	PER CENT
Ileocolostomy	31	12	39	75	21	28	106	33	31
Colocolostomy	28	12	43	130	41	31	158	53	34

Table VIII shows the type and frequency of the complications encountered. It can be seen that wound infections have been more frequent in the second ten-year period and deaths from peritonitis less frequent.

TABLE VIII. ANALYSIS OF COMPLICATIONS IN OPERATIONS WITH ANASTOMOSIS

COMPLICATION	1928 TO 1937	1938 TO 1947	TOTAL
Wound infection	2	17	19
Prolonged hospitalization (no specific complication noted)	3	7	10
Prolonged hospitalization for closure of cecostomy	2	11	13
Wound disruption	0	9	9
Abdominal abscess	7	2	9
Urinary tract complications	0	7	7
Intestinal obstruction	3	2	5
Fecal fistula	4	0	4
Pulmonary embolus	0	4	4
Pneumonia, atelectasis	0	2	2
Fever, undetermined origin	2	0	2
Thrombophlebitis	0	1	1
Total number of complicated cases			85
Total number of cases			264
Gross morbidity rate			32%

MANAGEMENT

Rankin[7] listed some "safety factors" to be observed in surgery of the colon. Those dealing with preoperative care are, (1) relieving obstruction, (2) combating dehydration, desiccation, and anemia during the preoperative period, (3) local cleansing of the bowel and eliminations of infections both by lavage and by chemotherapy, (4) evaluating the physiologic reserve of the patient based on laboratory evidence as well as physical examination and appearance. These are sound principles and must be observed if one is to carry out successful colon surgery.

As far as the technique of the surgery is concerned, we agree with those who say, "Less depends on the method used than on the manner of execution." Whipple[17] listed three principles to successful bowel anastomosis: (1) maintenance of adequate blood supply, (2) accurate apposition of serosa, and (3) avoidance of tension. These principles must be observed for successful surgery. It is felt that late leaks from an improperly executed suture line are most often responsible for peritonitis and intra-abdominal abscesses. In this series "open" and "closed" anastomoses, with and without special clamps, have been done. There results no demonstrable difference in mortality or morbidity.

Our present postoperative routine includes a duodenal indwelling tube which is left in place and connected to suction until the patient passes gas per rectum. Clear liquids only are allowed by mouth until intestinal motility is restored. Enemas are avoided. Whole blood, electrolytes, fluid, and protein are replaced as needed. Ambulation on the first or second postoperative day is encouraged unless there is specific contraindication to such activity. Rebreathing exercises with a paper bag, or hyperventilation with an oxygen-carbon dioxide mixture is used. Leg exercises by the patient when in bed are mandatory.

SUMMARY AND CONCLUSIONS

1. The records of all patients who have had definitive surgery for carcinoma of the colon, exclusive of rectum, at the Strong Memorial Hospital from 1928 to 1947 have been studied.

2. There were 264 patients who had a type of operation which involved a bowel anastomosis.

3. The gross, uncorrected mortality rate for the second of two ten-year periods has been 6.3 per cent.

4. Resection and anastomosis is our method of choice in dealing with carcinoma of the colon.

5. Preliminary or concomitant proximal drainage of the bowel has rarely been used in the cases with no obstruction. It is felt that the results here reported justify this policy.

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EXCISION OF THE MANDIBLE FOR NEOPLASTIC DISEASE

Indications and Techniques

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RESECTION of the lower jaw is not a common procedure, although it is an operation that has been a standard part of the surgical repertoire for many years. The infrequency of this operation is due to several factors, the principal ones being lack of understanding of the necessity for it in certain situations, and a natural reluctance to perform what is generally considered to be a mutilating and incapacitating removal of tissue. Furthermore, the mortality rate has been high and the cure rates low, the two approaching each other to the point of negation.

The angle of the mandible has been the "no man's land" of the surgical specialties, the general surgeon, the therapeutic radiologist, the plastic surgeon, the otolaryngologist, the oral surgeon, and the dental surgeon all meeting warily at this anatomic point, with the result that none has staked out a valid claim. Re-evaluation of the indications and techniques for excision of the mandible are in order, however, because of changing concepts of the reasons for such a procedure, and because recent advances in the ancillary surgical sciences have greatly increased the safety of such operations. Improvements in anesthesia and the development of antibiotics have together decreased the mortality and morbidity of this type of surgery to such an extent and as a corollary have so extended the anatomic limits of excision that a point of increasing returns has been reached.

It has, therefore, seemed worth while to review our cases in which partial, segmental, or hemiresection of the mandible was performed. Seventy-three patients are included in this study, sixty-nine of whom had excisional surgery other than biopsy. Four patients with tumors metastatic to the jaw, or with jaw involvement secondary to a systemic neoplastic disease, are included in the group because they are a necessary consideration in differential diagnosis of surgical diseases of the jaw. Many more patients referred for consideration of surgery are excluded because they were in a preterminal and untreatable condition, with such hopelessly far-advanced cancer that only palliative gestures could be made.

Tables I, II, III, and IV show the distribution of tumors in which excisional surgery of the jaw was considered. One is immediately impressed by the fact that tumors arising from the mandible itself constitute only a small part of the total group of tumor cases in which jaw surgery is necessary. This illustrates a recent and fundamental change in jaw surgery, namely, much greater emphasis on resections of the mandible in the surgical attack on intraoral cancer. Only 15 of our patients were operated upon for tumors arising primarily from the mandible itself, whereas 49 patients had

Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 24-26, 1949.

resection of the jaw for tumors arising in tissues adjacent to this bone. Of this last group, in 35 patients the jaw was involved by the tumor by secondary invasion and in 14 the jaw was not implicated but was resected as a necessity in the surgical approach to intra-oral cancer.

TABLE I. TUMORS OF THE JAW

Tumors of contiguous tissues adjacent to or involving mandible	49
Primary in mandible	15
Radiation damage to mandible	5
Metastatic to mandible	4
Total	73

TABLE II. PRIMARY TUMORS OF INFERIOR MAXILLA

Adamantinoma	4
Ossifying fibroma	4
Giant cell epulis	3
Osteogenic sarcoma	2
Central giant cell tumor	1
Eosinophilic granuloma	1
	15

TABLE III. TUMORS METASTATIC TO MANDIBLE

Multiple myeloma	2
Breast carcinoma	2
	4
INCIDENTAL DAMAGE TO MANDIBLE BY TREATMENT TO ADJACENT TUMORS	
Radionecrosis	5

TABLE IV. TUMORS OF CONTIGUOUS TISSUE ADJACENT TO OR INVOLVING MAXILLAE

Primary Carcinoma of:	
Gingiva	15
Tongue	12
Floor of mouth	10
Lip	6
Buccal mucosa	3
Submaxillary salivary gland	2
Skin	1
	49
35 involved jaw	
14 jaw free	
RECURRENT DISEASE INVOLVING MANDIBLE WITH LIMITED SURGERY	
17 patients all dead within 18 months of recurrent disease	

Primary Tumors of the Jaw.—The tumors arising from the jaw itself in this series are listed in Table II. Radicular cysts are not included. Although all possible jaw tumors did not occur in this series, it is representative enough to illustrate and to emphasize several important points. Most jaw tumors are not particularly dangerous, and are quite amenable to treatment. We should not accept a clinical and roentgen diagnosis of grave prognosis without biopsy proof and attempt at eradication. Four of our cases illustrate this well. One was a 4-year-old boy referred with a large painful swelling at the angle of

the right mandible, with a clinical diagnosis of inoperable osteogenic sarcoma. Roentgenologic studies revealed a large irregular osteolytic defect with pathologic fracture through the mandible. The clinical diagnosis seemed obvious, yet surgical exploration revealed the lesion to be an eosinophilic granuloma which has remained completely healed for five years following simple curettage. Three other patients had been allowed to develop huge tumors over periods of twelve to twenty years under the mistaken clinical impression that they were malignant and hopeless. All three tumors were benign ossifying fibromas and have been completely eradicated by resection of the jaw. Surgical measures of this extent would have been totally unnecessary if the lesions had been explored and defined microscopically early in their course.

The adamantinomas have been too long regarded as relatively benign lesions, of very slow growth, and incapable of metastasis. These considerations are not entirely correct, since admantinomas can produce tremendous destruction and very rarely one will metastasize and kill by secondary extension. Most of them are very slow-growing tumors, but they usually begin relatively early in life and after fifteen or twenty years of repeatedly inadequate therapeutic procedures, they usually have produced considerable deformity and suffering. It is our belief that this should be obviated by early recognition of the seriousness of the disease and treatment by segmental resection of the jaw and repair by delayed or immediate bone graft. Since adamantinomas arise in the alveolar ridge side of the mandible, it would seem unnecessary to sacrifice the enttre depth of the bone in all cases, and in early cases it should be possible to resect the involved area completely. This cannot be done by curettage, which is the usual ineffectual treatment. A planned excision of the area would seem to be the procedure of choice, but it has not been our privilege to encounter an "early" and previously untreated case of this tumor.

In the usual advanced and multiple recurrent adamantinoma, the tumor has been allowed to progress to a point where segmental or total resection of the jaw is required (Figs. 1 and 2). Careful roentgenologic estimate of the extent of bone involvement can sharply delimit the extent of excision of bone. Where full thickness of the mandible has been destroyed and soft tissues have been invaded, the tumor usually creates a pseudocapsule about itself by compression plus reactive fibrosis, so that its limits can be determined fairly accurately by palpation. These factors allow complete excision of the ordinary adamantinomas, whether they be early or far advanced. The fundamental premise in the treatment of adamantinomas is the cognizance that they will all create serious destruction and deformity if allowed to pursue their natural history.

The "ossifying fibroma" in our series is a tumor of as frequent occurrence as the adamantinoma. The salient features of these two tumors deserve equal emphasis because they are antithetical. Whereas the adamantinoma is a malignant lesion too often considered relatively benign, the "ossifying fibroma" on the other hand is a benign lesion whose growth po-

tential is too often considered to be malignant. Both errors have about equally disastrous results. The young fibroma is a discrete, circumscribed, and encapsulated tumor which can be excised completely without loss of jaw tissue. If not enucleated early in their course, they will continue to grow slowly until extensive deformity can result from pressure destruction of bone and soft tissues. The usual error in their recognition is pathologic interpretation of a biopsy as osteogenic sarcoma. Such a diagnosis usually eventuates in a fatalistic attitude of hopelessness so that nothing is done, and the patient ends up ten to fifteen years later as a derelict freak. Apparently the growth of these benign ossifying fibromas of bone is not biologically self-limited, as, for instance, are uterine "fibroids." The slow inexorable growth of these jaw tumors can create repulsive asymmetry, which could be completely and simply obviated early in their course by accurate definition of the lesion and adequate surgical management.

Fig. 1. Fig. 2.

Figs. 1 and 2.—Pre- and postoperative views of patient with adamantinoma of fifteen years' duration. Numerous incomplete excisions had been done, but by this time the tumor had so encroached on the oral cavity that severe interference with eating and swallowing was present. The entire left hemimandible was destroyed by the neoplasm which had invaded past the symphysis. Fig. 2. shows the patient with prosthetic upper and lower dentures in place which are satisfactory to the patient. Her criterion of success is that she can again eat popcorn.

Treatment of "ossifying fibromas" is entirely surgical, radiation being useless. In the early cases where the jaw has not been replaced by the tumor, they will appear as radiolucent, rounded, and usually unilocular osteolytic defects with spotty areas of calcification. Surgical approach to the mandibular tumors should be external, by turning up a curved neck flap with preservation of the lower (oral) branch of the facial nerve. The periosteum over the involved area of mandible should be stripped and preserved and the external table of the bone resected. The tumor can then be enucleated by careful dis-

section. The bone will regenerate surprisingly well, although in some relatively advanced cases precautions must be taken against pathologic fracture while healing occurs.

In the very advanced case, where the thinning of bone has progressed to complete destruction and replacement of the mandible by tumor, segmental resection is the only recourse (Figs. 3, 4, 5, and 6). It is this type of problem that should be prevented by early recognition and adequate surgical management long before such destruction takes place.

The giant cell epulis is a not infrequent benign tumor arising from the periosteum of the jaws. Clinical diagnosis is easy and the histologic picture is quite characteristic. Treatment is effective and consists of excision and curettage of the involved area of bone and periosteum, usually a relatively superficial and minor procedure.

The central giant cell tumor is a much more rare lesion, although its microscopic pattern is essentially similar. These tumors arise centrally in the jaw and will expand and destroy the bone, causing pathologic fracture. Our only instance of this tumor occurred in the horizontal ramus of a 19-year-old girl whose jaw was almost completely eroded by the growth. An intraoral approach and resection of the covering shell of bone, followed by wide curettage and irradiation, have resulted in a five-year cure with complete functional regeneration of the mandible on that side. Whether or not the irradiation was necessary is not known, but the analogy to epiphyseal giant cell tumors of long bones seemed reasonable.

Before any treatment of central giant cell tumors of the jaw is undertaken, appropriate studies should be made to detect hyperparathyroidism. In the upper jaw, particularly, giant cell tumors may be caused by such disturbed calcium metabolism, and local treatment in such an instance is both ineffectual and unnecessary.

Osteogenic sarcoma of the jaw is, fortunately, a rare tumor. Our experience is limited to two patients, both of whom were total failures of treatment. Both patients had been treated previously and had recurrent disease when first seen. These tumors usually kill by local extension rather than metastatic involvement, and it would seem that the problem in these cases is twofold: first, a more accurate pathologic appraisal of the lesion; second, a much more critical evaluation by the surgeon of the pathologist's report when the diagnosis is that of primary malignant bone tumor. These tumors, which kill by regional rather than distant involvement, are theoretically curable, but the surgeon must be well aware of the lethal potential of such a lesion when he assumes responsibility for its excision.

Tumors Involving the Mandible Secondarily.—The principal change in jaw surgery for neoplastic disease has been the marked increase in the surgical attack on intraoral cancer. Invasion of the mandible by carcinomas of the adjacent mucous membranes is far more common than the incidence of malignant tumors primary in the jaw itself. The resurgence of the surgical treatment of these situations has been due to two factors: first, recognition that it is practically impossible to sterilize squamous-cell carcinoma in bone by ir-

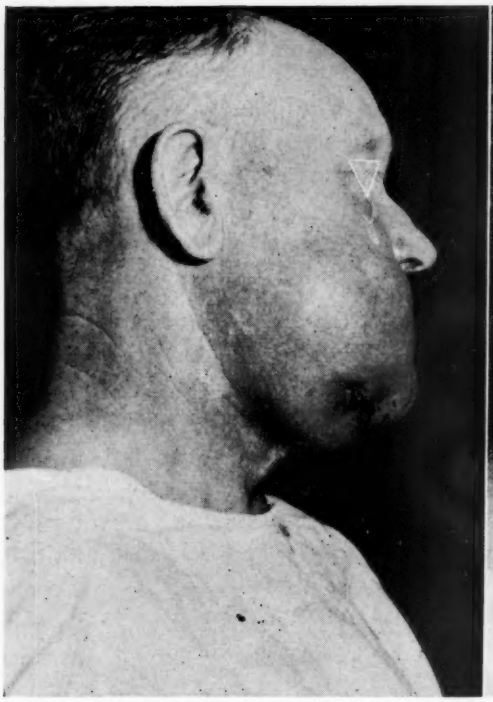

Fig. 3.

Fig. 4.

Fig. 5.

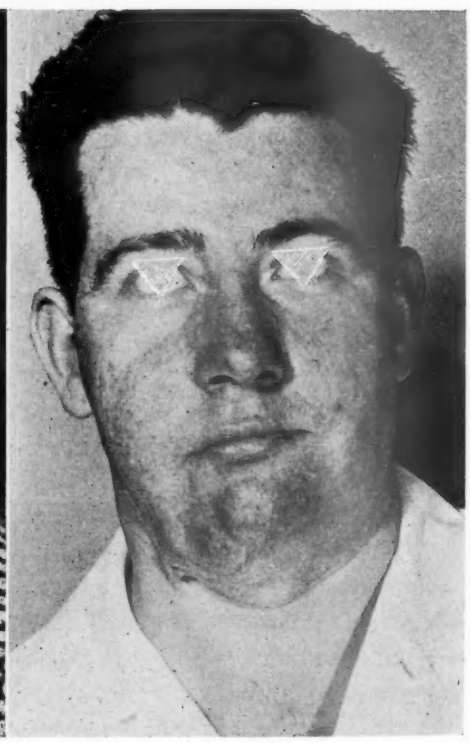

Fig. 6.

Figs. 3, 4, 5, and 6.—Pre- and postoperative photographs of patients with ossifying fibromas of twelve and sixteen years' duration, respectively. It was necessary in each instance to resect the horizontal ramus of the involved mandible because it had been completely replaced by tumor. Both patients have so far refused reconstructive procedures over periods of three and two years, respectively, since operation.

radiation methods, and that in the occasional case where this may be accomplished, the jaw will be so destroyed by the treatment that it will have to be removed anyway because of radionecrosis and osteomyelitis; second, advances in surgical techniques and anesthesia have allowed a much more radical operative attack with a reasonable mortality rate.

The advances in surgical technique are in two categories. Preoperative preparation of the patient is essentially the same nutritional problem as in pyloric obstruction or other major gastrointestinal surgery. Patients with advanced mouth cancer are frequently in as bad or worse condition than candidates for esophageal or abdominal surgery, and the same steps must be taken to correct protein deficiency, electrolytic imbalance, pan-avitaminosis, and anemia. The use of antibiotics has contributed tremendously to the safety of these operations, their use in the postoperative period being essential. The other phase of advance in surgical technique involves better anatomic concepts of the spread of intraoral cancer and of the possibilities for surgical elimination of the disease. The advances in plastic surgery have also greatly improved our techniques of repair. These phases will be discussed in further detail.

Advances in anesthesia technique consist essentially in improved methods of isolation and control of the airway, the use of the newer drugs, such as sodium pentothal, being of minor contributor importance. Intratracheal anesthesia is mandatory, so that the airway can be completely sealed from the operative field, blood and mucous secretions thus being blocked from access to the lung. The intratracheal tube may be inserted transnasally through the larynx and an inflatable cuff used to seal the trachea, or the pharynx may be packed with gauze after insertion of the tube. Both precautions are usually done. A preliminary tracheostomy may be necessary in some cases where trismus or tumor growth prevent intubation. This latter technique is used routinely in some clinics, and the anesthetic is then administered through the tracheostomy tube. Since a temporary tracheostomy is always required for the immediate postoperative period anyway, this last seems reasonable. There are some cases, however, in which operability of advanced disease cannot be determined except by examination under general anesthesia, and the authors have been able to avoid several futile major operations, let alone tracheostomies, by the routine of general anesthesia, intubation, examination in the operating room in doubtful cases, and execution of tracheostomy as the final step if the operative procedure is carried out.

The present surgical approach to intraoral cancer invading the mandible consists of a radical neck dissection on the involved side with removal of the hemimandible and all adjacent involved soft parts in continuity. Repair is immediate and a temporary tracheostomy is performed at the same time. The neck dissection is the usual formal en bloc dissection, with removal of the sternomastoid muscle and the internal jugular vein, but the excision of the jaw and intraoral soft parts allows considerable variation of technique according to anatomic extent of tumor invasion.

Historically the evolution of such a radical surgical technique and the reasons for it are of some interest. Bloodgood was one of the first to devise a limited operation through an external approach for excision of the jaw when involved by tumor of adjacent soft parts. The procedure was almost completely discarded because of the high mortality and low cure rates. Irradiation techniques improved so rapidly and seemed so promising that the use of radiation became the accepted and almost universal treatment of intraoral cancer—a situation which still holds today. With the extended use of radiation, techniques for intraoral excision of the mandible were developed of necessity for the resultant frequent radionecrosis. These were then applied to cancer involving or adjacent to the mandible, recurrent or persistent after irradiation. In the meantime the rationale and techniques for neck dissection were developed and became the treatment of choice for cervical node metastasis from intraoral squamous-cell carcinoma. Thus, the treatment of intraoral cancer was divided into two parts, irradiation of the primary being the usual procedure, and surgical treatment of the secondary cervical metastases being a separate consideration. In the meantime the development of the concept of the ideal cancer operation was perfected by many workers, Sampson-Handley, Halsted, and Meyer, to name a few, contributing the technique of the radical mastectomy. Miles in England devised the abdominoperineal resection of cancer of the rectum, and Cade has stated in general the principle of excision of the primary lesion, the intervening lymphatics, and the regional lymph nodes, as being the ideal cancer operation, exemplified by the operations just named. Pack[2] has aptly called this principle "excision and dissection in continuity," applied in his studies to surgical treatment of malignant melanoma. It remained for Martin[1] and his associates on the Head and Neck Service of the Memorial Hospital, New York, N. Y., to apply this concept to intraoral cancer, and they worked out the technique for the procedure outlined here. Grant Ward,[3] in a presentation before the James Ewing Society in New York in January, 1949, discussed his series of combined neck and jaw procedures and stated that he had done his first one twelve years previously.

Theoretically this concept of en bloc removal of the primary lesion, the intervening tissues, and the regional nodes, is more applicable to intraoral cancer than to many other tumors for one important reason: squamous-cell or epidermoid carcinoma of the oral mucous membranes has a very minimal tendency to invade veins and thus produce distant metastases. These tumors usually remain confined to the head and neck area and kill by local extension and interference with the airway, blood vessels, and food passages. This is in contradistinction to breast cancer with its marked propensity for venous invasion, or gastrointestinal cancer with the portal system and liver, and the peritoneal cavity as avenues of spread in addition to the lymphatics.

Prior to four years ago we did not have a single "five year cure" in patients with intraoral cancer invading the mandible, in fact the longest survival after treatment was eighteen months. Radiation patients were all dead within one year. At that time seventeen patients had been treated by lim-

ited surgery, either intraoral resection of the involved mandible, or staged combinations of partial or radical neck dissections plus excision of the mandible. This was sometimes done for local recurrence in the jaw, after neck dissection, a timing not of our choice. Table IV illustrates the results in this group of patients. Not a single patient was salvaged. At that time we applied the more extensive procedure of full radical neck dissection, hemimandibulectomy, and resection of soft part involvement plus tracheostomy as a one-stage procedure. At first only those patients with obvious excavation of the mandible and positive cervical node metastases were subjected to this procedure. Our first two patients so treated are now alive and well at the end of 3½ years. These patients recovered so well that the indications have been extended and to date thirty-two such operations have been performed. The salvage rate to date is shown in Table V. It is realized that this is too small a number to be of statistical significance, and no case is of five years' duration, yet the contrast to our preceding experience is so great that it is felt to be worth recording. In this type of cancer, a three-year survival is probably a valid cure rate, as

TABLE V. COMBINED OPERATION FOR PRIMARY OR RECURRENT DISEASE

ALIVE FREE OF DISEASE		
Free of disease:		
2		42 months
1		27 months
1		24 months
1		22 months
1		17 months
2		12 months
1		10 months
2		9 months
1		5 months
1		4 months
2		2 months
2		1 month
17		
ALIVE WITH RECURRENCE		
Alive:		
1		17 months
1		9 months
1		4 months
1		2 months
4		
DIED WITH DISEASE		
Died:		
1		24 months
1		18 months
1		12 months
1		11 months
1	(tbe)	10 months
2		9 months
1		7 months
1		5 months
9		
DIED POSTOPERATIVELY		
Died:		
1		3 days (age 86)
1		6 days
	(Both sudden cardiac failure)	

all our recurrences with one exception were apparent within ten months and averaged five months. The one exception had recurrence in the twelfth month.

Indications for the Operation of Combined Neck and Jaw Resections.—At the present time we consider the indications for this type of procedure to be in two categories, the absolute and the relative. The absolute indications would consist of clinical situations where squamous-cell carcinoma of the buccal mucosa, gingiva, or floor of the mouth has invaded the mandible by direct extension and has produced cervical node metastases. There is no way to salvage such a patient other than by radical neck dissection, excision of the hemimandible, and radical excision of the involved soft parts, all in continuity. Adenocarcinoma or muco-epidermoid carcinoma of the major or intraoral minor salivary glands can produce the same anatomic problem. Another absolute indication is postirradiation recurrence or persistence of cancer involving soft tissues adjacent to the mandible, whether or not the jaw is involved, and whether or not cervical node metastasis is evident. For extensive tongue lesions recurrent after irradiation, with or without clinically apparent cervical node metastases, this type of operation is also indicated, even though the mandible itself may not be involved by tumor. In these postradiation problems where the jaw is not involved, the tissues will not tolerate adequate further irradiation, and the jaw must be resected simply because it is in the way, there being no other adequate surgical approach compatible with the precepts of cancer surgery. The foregoing concepts apply in all particulars to carcinomas of comparable extent arising in the anterior palatal area, including the tonsil and adjacent pharyngeal wall.

It is believed that the considerations outlined here constitute absolute indications for the radical combined surgical attack on intraoral cancer. The relative or controversial indications comprise those clinical problems in which the carcinoma is not as far advanced and in which irradiation techniques are thought to have a chance of salvaging the individual. It may seem that the advanced stages of disease described as absolute indications for surgery are not common. When it is realized that the over-all cure rate of intraoral cancer in the best hands is about 25 per cent, it should be apparent that some 75 per cent of patients with this disease go through these advanced stages eventually, and at some time in their course they are theoretically still operable, and potentially salvageable by such radical surgery. The problem then is to choose the seemingly early cases which is not radio-curable and use surgery primarily. This question can only be answered by continued study of large series of cases, so that the margin of equivocal indications can be narrowed. It has been demonstrated that the combined operation is technically feasible, and offers some hope to patients with advanced intraoral cancer. It remains to apply the procedure to earlier cases in the hope that the over-all cure rate will be increased. If formerly hopeless intraoral cancer can occasionally be salvaged by this technique, it seems only logical that the poor cure rate of earlier cases could be improved by application of these radical surgical principles.

Technique of Combined Neck and Jaw Resection.—The skin incisions begin with a Kocher-type incision, curving downward and forward from the mastoid process to the hyoid bone and then upward to the midline of the chin. From the midpoint of this incision another is carried straight downward to the level of the clavicle, ending at the lateral border of the clavicular junction of the sternocleidomastoid muscle (Figs. 7, 8, 9, and 10). These incisions are carried through the platysma and then reflected posteriorly to the trapezius, and medially to the sternohyoid muscle or midline. The upper skin flap is dissected back to the level of the alveolar ridge of the mandible, unless the intraoral tumor involves soft parts lateral to the mandible and buccal gutter. The skin flaps, particularly the upper, can be varied considerably, depending on the individual problem of primary tumor location and extent.

After the skin flaps are mobilized the neck dissection is begun at the clavicular level and carried upward as a routine radical neck dissection. The tissues of the posterior triangle, the sternomastoid and omohyoid muscles, and the internal jugular vein are sectioned and reflected upward to the crossing of the hypoglossal nerve above the carotid bifurcation. The omohyoid is then cut away from the hyoid bone and the anterior portion of the submaxillary dissection is then effected, extending the dissection to the symphysis menti. The digastricus and stylohyoid muscles may or may not be sacrificed, as the local tumor problem requires. After the submaxillary area is freed from below, it is left attached superiorly to the undersurface of the mandible. At this point it is usually best to complete the upper posterior neck dissection, cutting across the upper portion of the sternomastoid muscle, usually also the tail of the parotid gland, and ligating and dividing the upper stump of the internal jugular vein. This portion of the dissection is then carried to a point just anterior to the angle of the mandible, leaving the entire neck dissection tissue attached to the undersurface of the horizontal ramus.

The upper neck incision is then extended through the midline of the lower lip into the mouth, and the mandible is sectioned in the midline with a Gigli saw. From this point considerable variation may be exercised, depending on the site and extent of tumor involvement. If the primary lesion is in the tongue and a hemiglossectomy is necessary, the tongue is split in the midline, and the excision carried back as far as necessary. If the tumor occupies only the floor of the mouth, the tongue is spared. If palate, tonsil, or pharyngeal wall is involved, excision is necessary. The soft palate can be removed at least to the midline. The amount of mandible removed depends on the extent of the tumor, but as a general rule the entire hemimandible is removed if the bone is invaded by cancer or if the lesion is posterior in the floor of the mouth, gingiva, buccal mucosa, or palate. If the bone is not invaded and the lesion is fairly well anterior, it is our belief that only the horizontal ramus need be removed. Preservation of the ascending ramus allows much better restoration by bone graft or prosthesis at a later date. After all condemned intraoral soft tissue is freed by incision, the mandible is then either disarticulated or sectioned at the indicated level and the surgical specimen, consisting of the cervical dissection, jaw portion, and intraoral tumor, is removed in one piece.

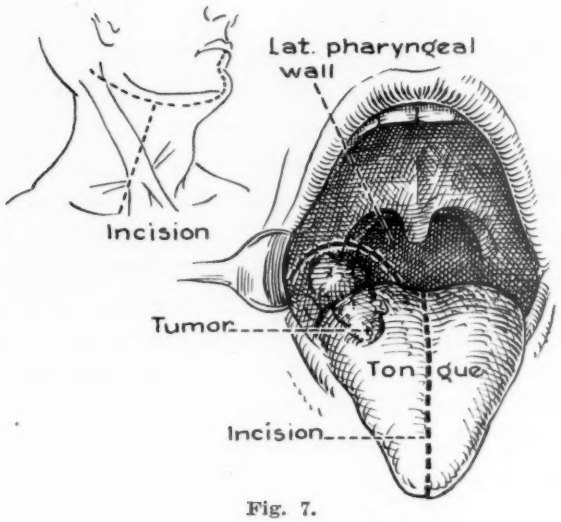

Fig. 7.

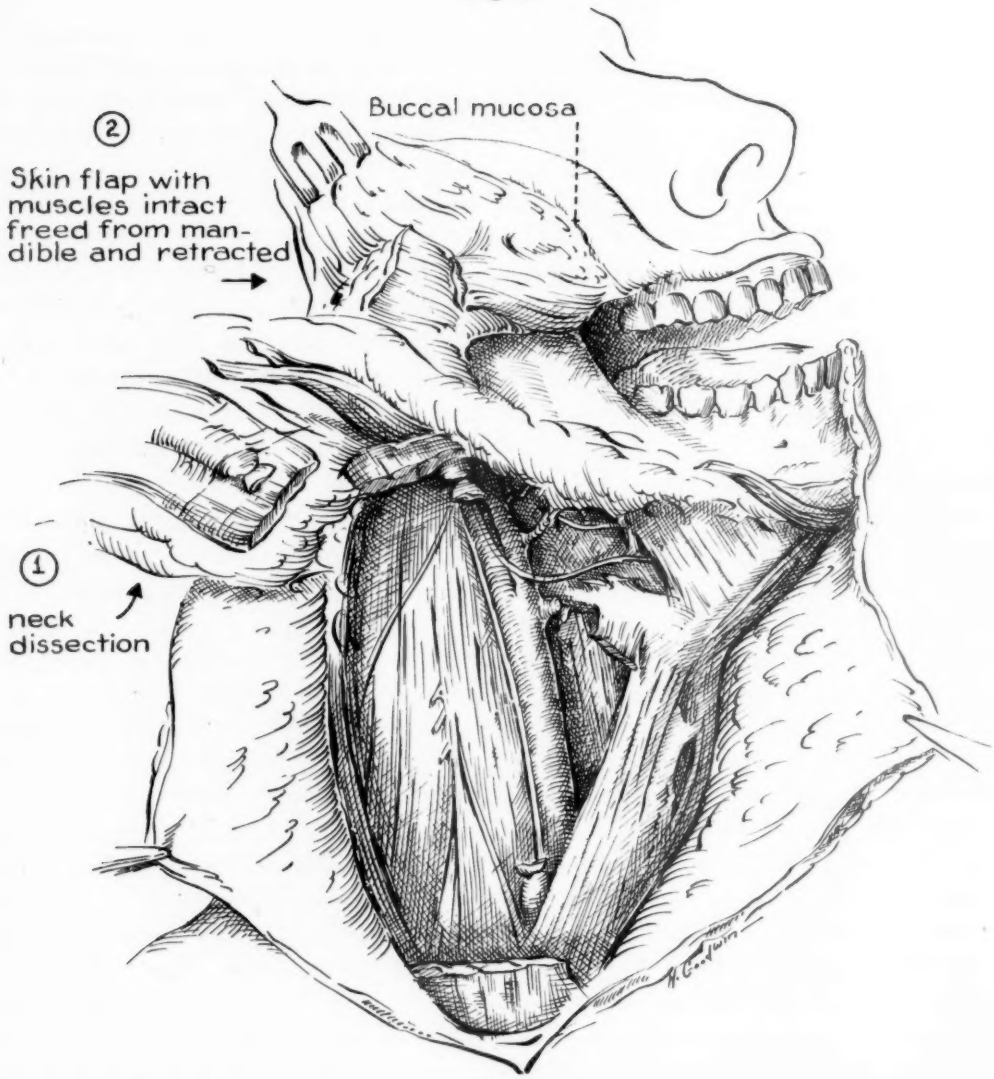

Fig. 8.

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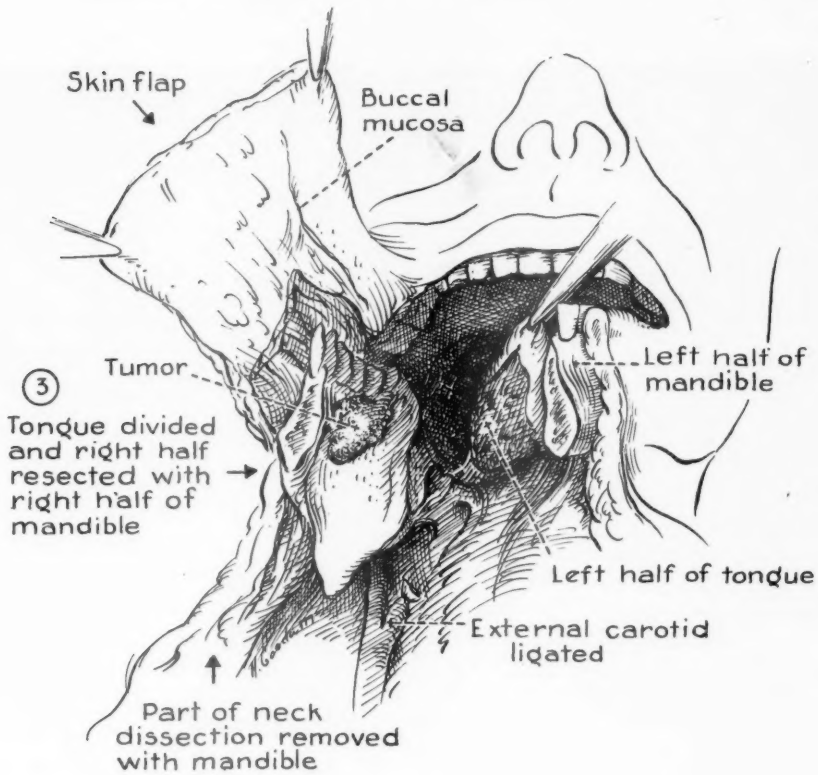

Fig. 9.

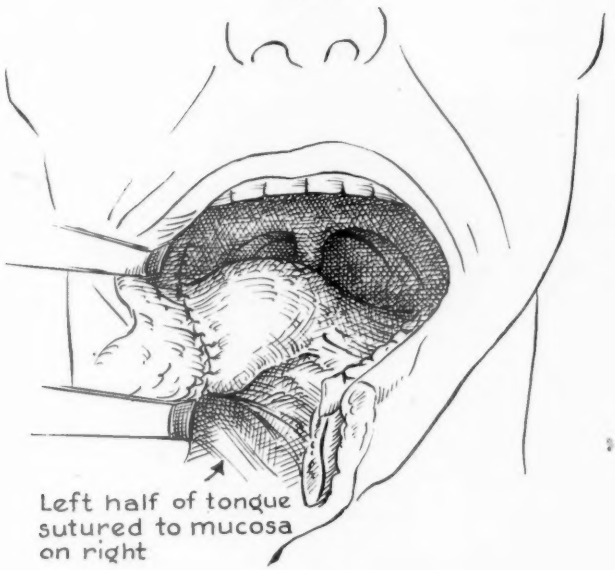

Fig. 10.

Figs. 7, 8, 9, and 10.—Diagrammatic presentation of the operation of combined jaw and neck dissection.

In Fig. 7 the upper insert shows the usual skin incision. The lower drawing shows the intraoral soft part incisions that can be utilized in the situation illustrated.

Fig. 8 illustrates the first stage of the operation as the neck dissection is completed. In the drawing the upper, or cheek flap, is raised to an exaggerated degree only for purposes of anatomic demonstration.

Fig. 9 illustrates the operative procedure after section of the mandible and incision through the midline of the tongue. Hemiglossectomy, of course, is performed only if the tongue is involved by the tumor, otherwise it is spared. After this stage the mandible is disarticulated or sectioned posteriorly at the required level.

Fig. 10 illustrates the primary step in closure, suture of the medial cut edge of the intraoral soft parts to the buccal mucosa lining the cheek flap. If a partial glossectomy has been done as shown here, the tip of the tongue should be left free if possible and the tip reconstructed by sutures. This will greatly facilitate tongue function and improve the linguals in speaking.

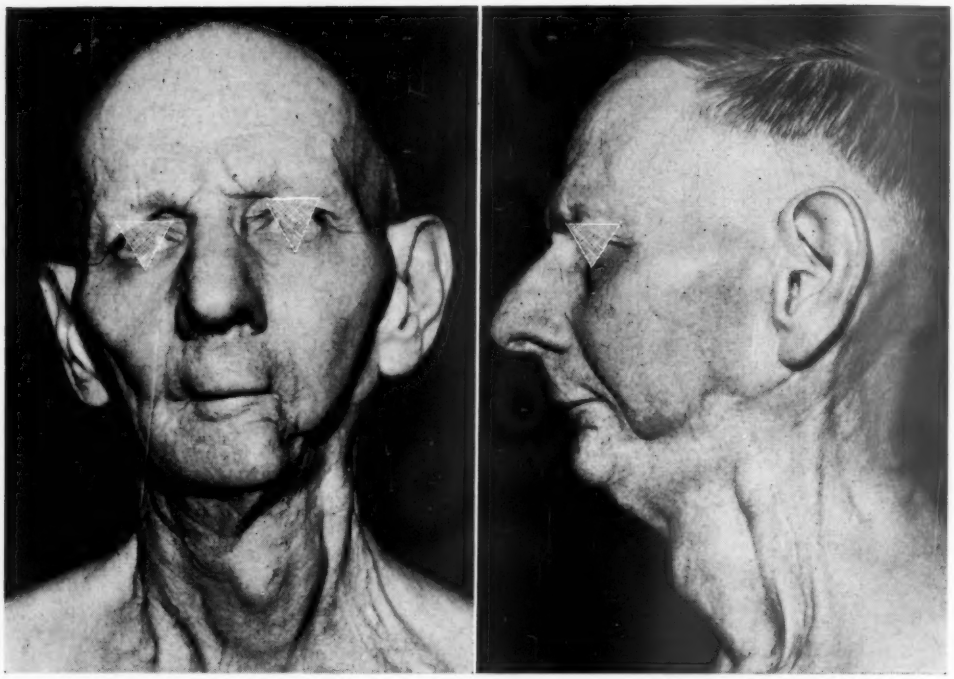

Fig. 11. Fig. 12.

Figs. 11 and 12.—Anteroposterior and lateral views of postoperative condition of 78-year-old man who had a carcinoma of the left buccal gutter which involved the commissure and ulcerated through the cheek externally. The mandible was deeply excavated and there were cervical node metastases. A combined jaw and neck dissection with excision of full thickness of the cheek and angle of the mouth was performed one year ago in April, 1948, and the patient has remained well to date.

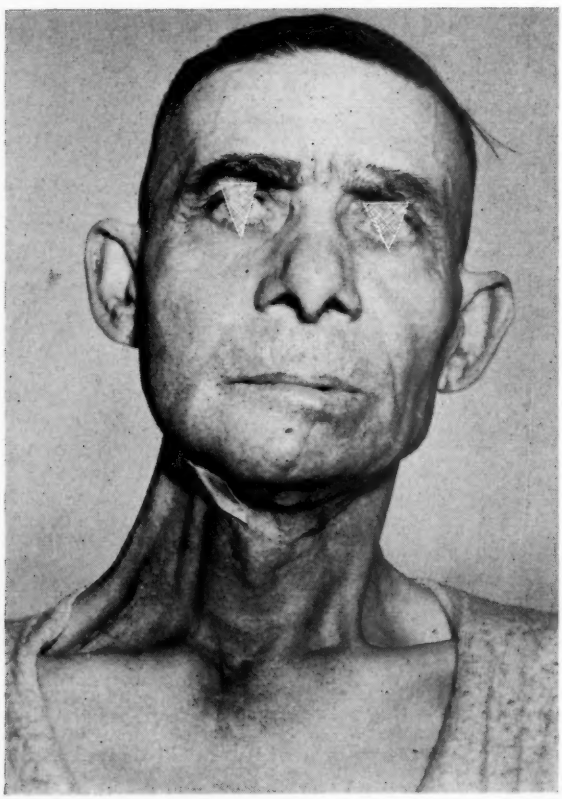

Fig. 13.—Postoperative appearance of 63-year-old man who was operated upon in January, 1948, for a recurrent cancer of the palate, involving the jaw, and with cervical node metastases fixed to the mandible. There was radionecrosis of the intraoral soft tissues and trismus so complete that nutrition was poor. A combined soft part, jaw, and radical neck dissection was performed. Note minimal cosmetic defect. He has remained well to date, twenty months after surgery, and has been working at his usual job.

Reconstruction is accomplished by suturing the medial cut edge of the oral mucosa, whether it be remaining floor of mouth or sectioned portion of tongue to the buccal mucosa lining the upper skin flap. This reconstitutes the oral cavity, and isolates the mouth from the cervical dissection area. Careful technique here, with double layer interrupted suture line, will usually result in a watertight closure and primary healing. The frequent problem, however, of having to work with irradiated tissues may result in a breakdown of healing and resultant oral fistula. Such a contingency is of minor importance in the neck as compared with a leak in an intraperitoneal bowel closure. After the mouth closure is effected, the skin flaps are approximated with two or more Penrose drains strategically placed. A tracheostomy is then performed, if it has not already been done.

DISCUSSION

Two separate problems have been presented in this study of our experience in resection of the mandible for neoplastic disease. The surgical treatment of tumors primary in the jaw is an entirely different exercise than the resection of this bone in the surgical attack on advanced intraoral cancer. In the latter situation the mandible is simply a portion of the en bloc resection which includes the intraoral primary tumor, the regional lymph nodes, and the intervening lymphatics. In this respect the mandible is implicated in three ways: it may be infiltrated by cancer by direct extension; its periosteum through which passes a large portion of the lymphatic channels from the gingiva, buccal mucosa, and floor of mouth may be closely associated with the primary cervical metastatic lesions; the jawbone may simply be a structural barrier to surgical access to intraoral cancer from any direction, and an architectural obstruction to soft tissue repair.

This last consideration has been one of the main obstacles in acceptance of resection of the mandible for intraoral cancer, particularly when the bone itself is not directly invaded. The resultant cosmetic and functional defects have been greatly exaggerated in the minds of those surgeons who have neither performed such an operation nor personally followed the victims of intraoral cancer to their death. There is no more cruel death than that from head and neck cancer, the distribution of sensory end organs in the body being in all respects what it is. The problem of plastic reconstruction of these patients is important, but it is secondary to the problem of curing cancer. Our patients have invariably been grateful, and those who had recurrence after such surgery have had significant palliation.

The degree of palliation achieved by radical surgery in advanced intraoral cancer has been an unexpected dividend. It is chiefly due to interruption of the cervical plexus and third division of the fifth cranial nerve, plus the removal of ulcerating infected and frequently necrotic cancer in the mouth.

As yet there has been no difficulty in gaining consent of the patient for radical surgery. Most of the patients have been so miserable that they have acceded willingly to any suggestion. When the operation of combined neck and jaw dissection is applied to patients with relatively early lesions, as log-

ically it should be, such recommendations must be based on more critical evaluation than is possible at the present time.

Restoration of normal functions and symmetry after a combined neck and jaw dissection is not as urgent a problem as it might seem. The primary repair results in a functional state which is not only compatible with maintenance of nutrition but usually allows weight gain and recovery to a normal condition. Our surviving patients have all been improved by the operation and all but two have refused bone graft restoration. It is our impression at the present time that the plastic reconstruction of these patients is entirely secondary to the problem of eliminating cancer. Procedures for reconstruction of the jaw, such as primary bone graft, or the insertion of steel or Vitallium bars, compound an already complicated problem in healing, and may obscure recurrence of cancer during the follow-up period. This last is not actually very important, because when cancer recurs after a combined neck and jaw dissection there is, of course, little or nothing that can be done further toward cure. Another obstacle to immediate attempts at restoration of bone continuity is the hazard of working with irradiated tissues. Most of our cases having radical surgery have had prior irradiation to an extent that healing of the surgical repair is embarrassed. In a contaminated field, and working with radiation damaged tissues, we have hesitated to add a foreign body to the already difficult problem of tissue repair.

Most patients with intraoral cancer are in age groups in which function is paramount to appearance. So far it is our experience that a dental prosthesis is the most practical compromise for those patients who have had a resection of one half of the lower jaw. Many of these individuals are content to leave well enough alone and will not bother with prosthetic dentures. It is not our purpose to minimize the importance of plastic reconstruction, but rather to assign it a proper place in relation to cancer.

SUMMARY

A review of our experience in tumor surgery of the jaw has been presented. It is apparent from this study that tumors arising from the bone itself are in the minority. The major considerations at present are secondary involvement of the bone by intraoral cancer arising in the soft tissues, and the newer concepts of surgical attack on intraoral cancer which require excision of part or all of the hemimandible, whether or not it is directly invaded by tumor. The operation of combined neck and jaw dissection is described and an interim evaluation of it is presented.

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QUARTERECTOMY—ITS APPLICATION IN MALIGNANT MELANOMA

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MALIGNANT melanoma has achieved a reputation among surgeons for being one of the most hopeless of malignant tumors, which has resulted in a spirit of defeatism permeating the minds of the professional public. While it deserves a place in the scope of serious malignant disorders, it remains that it is much more amenable to therapy than, for instance, carcinoma of the stomach and lung; its reported five-year cure rate averaging about 20 to 25 per cent,[1] where in the case of the stomach and the lung the rate is much lower—5 to 10 per cent at best. Also, the lesion is most often located in a position where it can be observed, diagnosed earlier, its extensions and metastases are more accurately established, and the application of radical surgery with wide margins more definitely accomplished. Therefore, the modern idea of hopelessness is not a justified concept.

The problem today is simply to learn why surgery has not, in a malignant tumor so susceptible to radical treatment, elevated the survival rate of these patients. The truth can be learned only by a study of our past experience in the treatment of this condition, sifting out possible defects of our therapy and attempting to correct what we may be doing that is wrong. It is irritatingly tantalizing to view these tumors, so far removed from vital structures at their conception, and realize that with our present methods we cannot arrive at a better survival rate. They arise in the skin, its appendages, or some epithelial structure not so obscure. The medical profession has learned the danger of the black mole, its growth and extensions, and is seeking the aid of the surgeon much more rapidly. If surgery is a proper method to cure this disease, surgeons have not demonstrated their ability to achieve good results. Radical surgery has proved its place in the most successful of procedures to rid the body of malignant disease and, until some superior chemical, electrical, or biologic method is evolved, must be employed if we wish to better our results. Some of the defeatism exists in the fact that radical surgery has been employed when the condition is far beyond any aid surgery could possibly afford.

Melanoma demonstrates one of the characteristics of malignancy beautifully, namely, the fulminating and the nonfulminating nature of the tumor. Pathologically, one cannot prognose which melanoma will be a fast killer and which one is slow growing or nonfulminating. Figs. 1 and 2 clearly demonstrate this fact. The histologic structure of Fig. 1 appears to be a much more rapidly growing tumor than that in Fig. 2, but the first patient lived one year

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Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 24-26, 1949.

and nine months after the onset, whereas the second patient lived a period of only four months. The criterion that has appeared to be significant in the 33 patients seen at Kennedy Hospital in the past two and one-half years has been the rate of growth observed by the patient and his physicians, which has been obtained in the history. This has proved most reliable in every

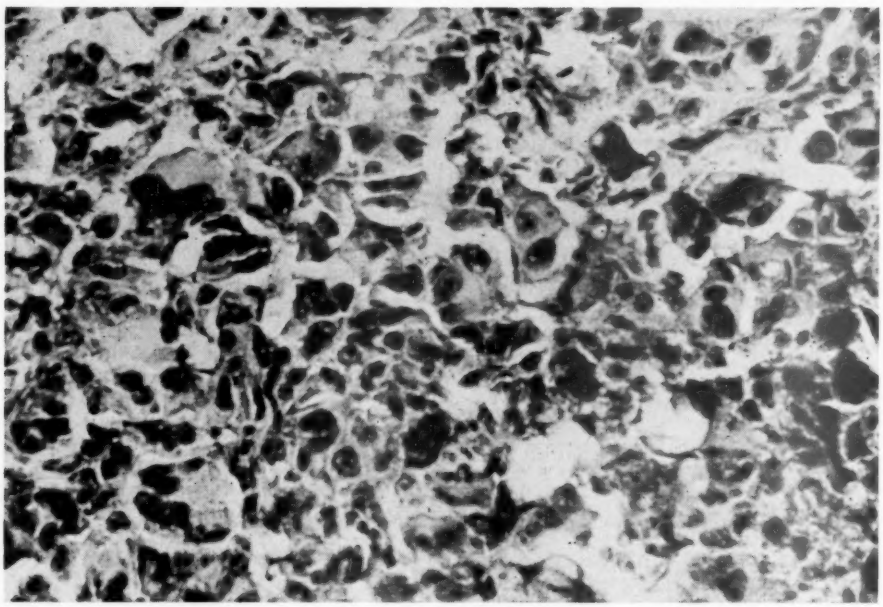

Fig. 1.—Picture of a rapid-growing melanoma; patient survived one and three-quarters years.

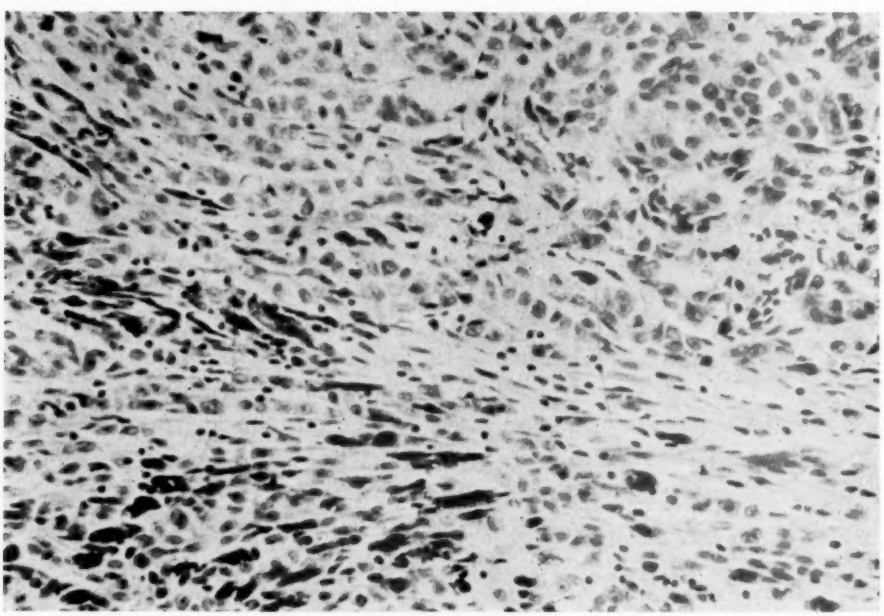

Fig. 2.—Relatively benign-looking histologic picture of melanoma; patient survived four months.

instance, with the possible exception of those arising in the eye. Advanced age of the patient appears to be a retarding influence on the growth, but cannot be relied upon in many patients. Another observation about fulmination exists in the known slow-growing melanoma. We have observed several with a history of slow growth, apparently responding to surgical treatment, and, suddenly, after appearing to be under control for a period of as much as four years, become fulminating with rapid fatal spread in the course of a few months. In this respect the incidents suggest that the natural course of the tumor or surgery itself has been a dam which successfully controlled the flood water up to a certain period, when the dam finally and precipitously gives away.

In reviewing our cases it appears that our surgical efforts in this fulminating group or in the group which after a period of relative benignity assume the fulminating role have been futile. Not a single case has shown a favorable response to surgery, and when this fulminating characteristic is manifested beyond a question of doubt, we do not employ surgery in these cases. For instance, a 20-year-old patient entered the hospital with a large mass of involved glands in the right groin subsequent to his observation that a mole appeared at the lower portion of the right thigh. The time element from first recognition until hospital admission was three months. He was anemic, cachectic, and weak. X-ray examination failed to reveal metastases. No nodules were noticed elsewhere. Ordinarily we would have performed hemipelvectomy with dispatch, once the melanoma was verified by histologic study. After one week's observation the groin masses enlarged rapidly, could be felt along the iliac vessels by rectal palpation, and his general condition became worse. His family insisted upon taking the patient to his home when informed of the fulminating, surgically hopeless condition, where he died three weeks later, exactly four months from the time of onset. It is our contention that in a case of this sort, surgery is futile and should not be employed. We hesitate, of course, to admit it but surgery in this type of case fails, and a simple study of the details of the history tells us why. The case histories which follow demonstrate the indication for treatment of the slow-growing melanomas and need not be repeated here. There are no reports from any source which have suggested any degree of favorable response in this type of fulminating case. As soon as the nonfulmination of the case is established, we must then turn to the type of treatment which is most efficacious.

In seeking the type of treatment one is striving for a method that will produce as good results as the ophthalmologists have achieved in melanoma arising in the eye. The early lesions are simply treated by enucleation, which effects 90 per cent five-year survival rate. When the periocular space is invaded, however, exenteration effects a five-year cure rate of 20 to 30 per cent, exactly the same figure pervading general surgical experiences. Callender[14] has attempted to parallel prognosis with the pathologic picture, and after the examination of 500 melanomatous eyes believes that there are four types and that longevity depends upon the pathologic type. There is also disagreement

amongst pathologists in respect to eye melanoma. Some believe it is a different tumor from melanoma located elsewhere in the body. Others vigorously declare that these eye tumors are the same as those existing in other parts. However, the facts suggest that when melanoma arises in the eye at a site which impairs vision, consultation is prompt and definitive operation is performed much earlier than in the general surgical lesions; and when the melanoma arises at a site which does not affect vision, the operation is tragically delayed and the results then compare with the general surgical experiences. This presupposes that with early recognition of a limb, body, or head melanoma, wide local excision should suffice to achieve the excellent rate obtained by the eye surgeons. This, unfortunately, is not true.

A brief perusal of the various methods of surgical procedures is in order.

Preventive Surgery.—This method has been employed for years, heralded by explosive propaganda, and has resulted in a scramble for the urgent removal of moles after a lecture heard by students, nurses, laity, and physicians. After a while the panic disappears and the moles are regarded nonchalantly. Bloodgood[2] removed and studied 300 moles, none of which were malignant. He believed, however, that he could predict which moles would become malignant and, therefore, which ones should be removed. Each person averages 20 to 30 moles; some have greater numbers, but when multiplied by the number of people in the world, there must be in the neighborhood of 30 to 40 billion moles in the world population. The number that are or become malignant must be infinitesimally small compared to the total number. A de-moling of the population is, therefore, impractical. Ackerman[3] has stated the generalities about the relation of moles to malignancy in a practical manner. He comments upon the general benignity of the raised brown mole and the hairy mole, that moles above the umbilicus are less dangerous than those below it, that the dorsum of the foot is a very dangerous place for a black mole, that moles in sites of frequent irritation are vulnerable, etc., and one can gain from his dicta a sensible approach to the problem. The deeply pigmented mole in the child will usually not be dangerous until after the age of puberty. One point is clear. It is not known how many melanomas are aborted by preventive mole removals, if any, although oncologists and propagandists intimate triumphant results by this maneuver. Nevertheless, preventive removal should not be unduly discouraged. It is an interesting sidelight in 1949 to recognize the castigation leveled at the surgeon, dermatologist, and early oncologists when melanoma seemed to sprout following the removal of a mole. We now know that these moles were malignant before removal or partial extirpation.

Local Excision.—There is little need for comment about the procedure of local excision. Melanomas have been excised locally, with or without great margin, with uniformly poor results. Surgeons are well aware of the defects of this method because it was the earliest method employed, and today one sees patients who have had local excision due to improper diagnosis and inexperience of the operator. All competent students of this disease con-

demn local excision because of its known failures. However, several of our patients survived three to four years after local removal before extensions or metastases appeared. In these cases melanoma was found thriving at or near the original site as well as in the distant metastatic areas. Reflection about the course of these cases suggests that these particular tumors were nonfulminating, and the experiences may afford a clue to the proper treatment. To us, it means that if an extremely radical procedure had been employed at the time of the original operation instead of local excision, not only five-year survival, but permanent cure may have been established. This last statement is actually the concept upon which basis quarterectomy is favorably considered in the treatment of this disease.

Local Excision Plus Regional Glandular Dissection.—A method now commonly used consists of removal of the local lesion widely and deeply, repairing the local defect by grafting, and at a later date, supposedly allowing enough time for the malignant cells in the lymphatics to reach and be trapped in the regional glands, radical regional glandular dissection is performed.

To illustrate, a 55-year-old man appeared with a small melanoma of the scalp, in the right temporal region, of seven months' duration. The lesion grew slowly and became ulcerated. No palpable cervical glands were present.

Operation was a radical excision with a skin graft to the area. Three weeks later a radical gland dissection of the right side of the neck was done. No melanoma was found in any cervical nodes.

This seems to be a proper operation for a lesion in this site. The lymphatic drainage is possible through the channel anterior as well as posterior to the ear. Total excision of the channel is not practical and, of course, amputation cannot be done. Unfortunately, this procedure does not show much improvement over local wide excision, but Ackerman[3] stated that the results of this type of surgery suggest about 38 per cent five-year survivals in a small group of selected cases, which is better than the original 25 per cent. Unquestionably, it is suggested that if this procedure is employed very early in a nonfulminating case, one may expect better than the existing survival rate. The great disadvantage of this operation exists in the fact that one cannot totally extirpate the disease along with its lymphatic drainage without cutting across the lymphatics or traumatizing the nodes which may contain microscopic foci of the neoplasm. Therefore, this operation is proper only when the more radical approach is not allowable.

Local Excision Plus Removal of the Lymphatic Drainage Tract and Its Regional Glands.—The method of local excision plus removal of the lymphatic drainage tract and its regional glands sprung from Handley,[4] polished and highly advocated by Pringle,[5] and popularized much later by Pack[6] and a few others. It is more radical than the previous procedures and one can begin to notice perhaps longer survivals by this method, but the results are not so convincingly good that one does not question the use of a more radical procedure. Not enough cases have been observed for long periods to be certain of its efficacy.

The procedure is best illustrated by report of a 34-year-old man who recognized an abnormal black mole on the inner surface of the right thigh. It was present four months when an experienced surgeon recognized the tragic importance and transferred the patient to Walter Reed General Hospital promptly. Two days later the thigh and groin were prepared and draped. The tumor was removed with a two-inch margin from its borders and deeply enough to include the fascia lata. Microscopic study confirmed our suspicions of the malignancy of this melanoma. Consequently, a wide tract of skin, subcutaneous tissue, and fascia were excised in continuity. The procedure extended from the local site upward with radical removal of the femoral, inguinal, and iliac nodes to a site well above the hypogastric artery, removing with the mass the femoral vein. It was necessary to incise Poupart's ligament to gain proper exposure. No melanoma could be demonstrated in the excised glands. The patient is free of demonstrable disease by a thorough metastatic survey done at Kennedy Hospital three years and four months postoperatively.

In another case, similar to the Walter Reed case, the patient has survived three years and five months without noticeable disease. This Handley procedure certainly is the method of choice for melanoma of the trunk. Pack has performed the operation on several patients whose lesions resided in the axillary line about the level of the umbilicus. In these instances he has dissected the axilla, groin, and wide tract containing the tumor and its likely lymphatic channels in continuity and in one stage. It has the disadvantages of cutting across possibly involved lymphatic channels and of traumatizing by manipulation the nodes bearing microscopic foci. However, this operation better fulfills the idea of radical surgery than the other procedures.

Amputation With or Without Regional Glandular Resection.—High thigh or arm amputation has been utilized in the past more than we realize, and it has notably failed except in one instance, namely, the more favorable subungual melanoma. The slow course and relative benignity of melanomas which arise under the finger- or toe-nails are well recognized. Many reports of long survival in this group indicate that a proper method may be local toe or finger amputation, followed by regional gland dissection. In these subungual cases more radical procedures are not indicated with our present knowledge unless disease is discovered in the limb in the postoperative studies. For melanoma of the dorsum of the foot, leg, or thigh, ordinary thigh amputation with or without gland dissection is to be condemned. I remember a case where amputation was performed for melanoma of the dorsum of the foot of short duration. Groin dissection was performed shortly after the amputation. The patient returned to the Cincinnati General Hospital four and one-half months after the amputation with large clusters of melanomatous tumor residing in the amputation incision. Obviously melanoma cells must have been present in the lymphatics at the time these channels were incised during the amputation, and once seeded in the tissues of the stump, thrived vigorously. Other cases of amputation in similar sites revealed glandular

involvement or distant metastases in short periods of time following operation.

When these considerations are perused, pessimism can be lifted only if more radical early surgery can be evolved. The prominent factors in more radical surgery demand an operation that will in one sweep remove the local lesion, all of its lymphatic vessels, and the barrier nodal drainage without manipulation of the lesion, its tracts, or barrier. Melanoma teaches the surgeon better than any other malignant tumor not to traumatize or manipulate the tumor because these acts may inevitably result in malignant spread. Holman has stressed this point in student examination of the cancerous breast. I performed radical neck dissections upon two patients with melanoma of the face who had been subjected to aspiration biopsies of involved nodes approximately ten days prior to operation. Great astonishment was manifested by all who examined the resected material when it was observed that a black path existed between the aspirated gland and the point on the skin where the needle was inserted. These paths demonstrated the presence of malignant cells when examined microscopically.

To meet the demands of this radical approach, quarterectomy seems adequately to fulfill the principles. This means interscapular amputation of the arm and hemipelvectomy for the leg cases. These are mutilating procedures, not desirable, and would be tragic unless employed for the saving of life when no other procedures will suffice. Properly employed, the procedure does not include the operator's manipulating the tract or nodal barrier. The virtue of this type of operation lies in the fact that the nodal area is resected radically en bloc with the lymphatic pathways and local site. These radical amputations are accepted by the profession for other malignant tumors, especially osteogenic, fibrosarcomas, and neurosarcomas, but have not been employed for early melanomas. Pack[8, 9] has advocated hip joint disarticulation combined with regional gland dissections in some selected cases of melanoma of the thigh, but mainly when he did not feel that excision in continuity was feasible. He has not advocated this radical procedure in the early case. Hip joint disarticulation and gland dissection does not meet the degree of thorough radical surgery that this malignant tumor requires. First, because the incision encircles the upper part of the thigh, which necessitates cutting across involved lymphatics entering the nodal barrier. Second, the nodal barrier is manipulated and this coexistent trauma to involved glands may dangerously effect a spread of the tumor. Third, it does not permit resection of the iliac nodes without undesirable manipulation. Fourth, the incision is directed in the fibers of Poupart's ligament, which is too close to the nodal barrier for radical surgical comfort. Last, hip disarticulation in itself is a mutilating procedure, not much more mutilating than hemipelvectomy. It has one advantage only over hemipelvectomy, that it allows a poorly functioning prosthesis, which is impossible to date following hemipelvectomy. Pack[10] stated in one article that he performed hemipelvectomy in two cases of melanoma, but the details of the cases are not given.

The incision I employ in hemipelvectomy for melanoma begins anteriorly above the iliac crest and extends to the pubis in a semicircular fashion which

includes approximately three inches of skin and subcutaneous tissue above Poupart's ligament. A deeper incision in the muscle layer includes a transection of the muscles approximately three inches above Poupart's ligament. Peritoneum is reflected medially. If there are no involved nodes above the hypogastric artery, the external iliac artery is ligated and the remainder of the anterior work accomplished before the iliac vein is tied. The iliac artery and vein are transected just below the hypogastric artery and the nodes and areolar tissue below this point are not dissected but are removed with the resected quarter. Therefore, the nodal and lymphatic channels are amputated at a distance well above the femoral regions without any manipulation of the tissues in that vicinity. We, therefore, felt justified in advising quarterectomy for melanomas early, preferably before the main nodal barrier became involved, and have employed the procedure in four cases, three involving the leg and one the arm. The postoperative period is not long enough to be suggestive, but the rarity of the tumors requires that several clinics study the results in quarterectomy so that significant data can be collected. The gross findings of the resected quarters constitute evidence which may predict more favorable outcomes than we have observed by less radical methods.

Preoperative Studies.—These are extremely important, because the mutilation would not be justified except in those cases where, after thorough study, it is believed that the disease has not progressed beyond the nodal area available for resection. It involves thorough history and physical examination which searches for glandular involvement and subcutaneous nodules from the top of the head to the toes. If any suspicious nodules are observed, removal and histologic study must be performed. X-ray examination of skull, chest, spine, and long bones must be included in the study. These studies require only a few days and should be completed with dispatch. One is always aware of the possibility of blood stream spread and there is no accurate method of determining this at any one period, unless the history of fulmination is at hand. Melanin in the urine or blood is not an accurate indication of metastases. For instance, we have seen melanuria in a favorable case, where the extensively involved case with widespread metastases may not reveal the presence of the melanin in the urine. We have also observed that in a given case, melanuria is likely to be intermittent and its existence is therefore of doubtful significance. However, if a case seems to be a favorable one, procrastination about the possibility of blood stream spread is unimportant, because if that type of spread has unknowingly already occurred, quarterectomy will not materially add to the patient's dilemma, because his life span will not be long. Also, mentally it may benefit the patient to know that a definite radical procedure has been performed in his behalf.

The important gesture in the preoperative studies is the biopsy and the manner in which it is obtained. Once the patient enters the hospital, the patient, nurses, attendants, and inexperienced surgeons are warned about trauma to the lesion or its lymphatic involvements. We consider the biopsy of major importance. If melanoma is seriously considered, the local lesion is excised in

toto with a large margin in all directions and the resultant defect immediately skin grafted. Unfortunately, most of our patients have been "cut into" before arrival at the hospital and this trauma has not been avoided. Two or three days later when the pathologist is certain of the malignancy, the radical procedure is performed. It is our belief that a cardinal sin would be to incise or remove an involved lymph gland unless that is absolutely necessary. If the local lesion has been removed previously or the enlarged glands are the result of gastrointestinal melanoma, then glandular biopsy may be in order, but in all five cases presented here, the local lesion gave the answer, and the glands were not traumatized except in the last case and that had been done prior to admission to Kennedy Hospital. Until we are more confident as we obtain experience in this radical procedure, we prefer not to perform quarterectomy from frozen section alone, although that may ultimately be the procedure of choice. One reason is the effect upon the patient. It is difficult for a patient to grasp the seriousness of the situation at first. The permanent histologic study has aided this phase of the problem, because the patient is aware of the fact that the positive information obtained is trustworthy in all respects, has grasped the enthusiasm for radical surgery, and feels resignedly hopeful.

Fig. 3 (Case 1).—Amputated quarter; note heel lesion.

MELANOMA CASES

CASE 1.—J. H. M. was a 59-year-old diabetic patient. This arteriosclerotic white man was admitted to Kennedy Hospital, April 7, 1948, complaining of an ulcer on the right heel of five months' duration. The black ulcer gradually became larger, but was not painful. There was a small mass in the right femoral region. Biopsy revealed melanoma. After regulation of the diabetes, right hemipelvectomy was performed on April 19, 1948. There was moderate shock, but the patient tolerated the procedure well. There was wound infection and slough of the muscles in the posterior flap. This responded to local therapy, although

a draining sinus is still present. Seventy-nine days after operation, homologous serum jaundice appeared from which the patient promptly recovered. Examination of the resected quarter revealed melanoma of the heel, with metastatic involvement to the right femoral nodes. Lymph nodes above the femoral region were enlarged, but were free of malignancy, demonstrating only lymphoid hyperplasia upon pathologic study. He remained in the hospital for a period of five months. X-ray examinations of pelvis and chest were made at regular intervals, but there was no evidence of metastases.

Follow-up Study.—Ten months postoperatively, draining sinus persisted. There was no evidence of melanoma in the flaps. There were no metastases. The patient was residing in a domiciliary home.

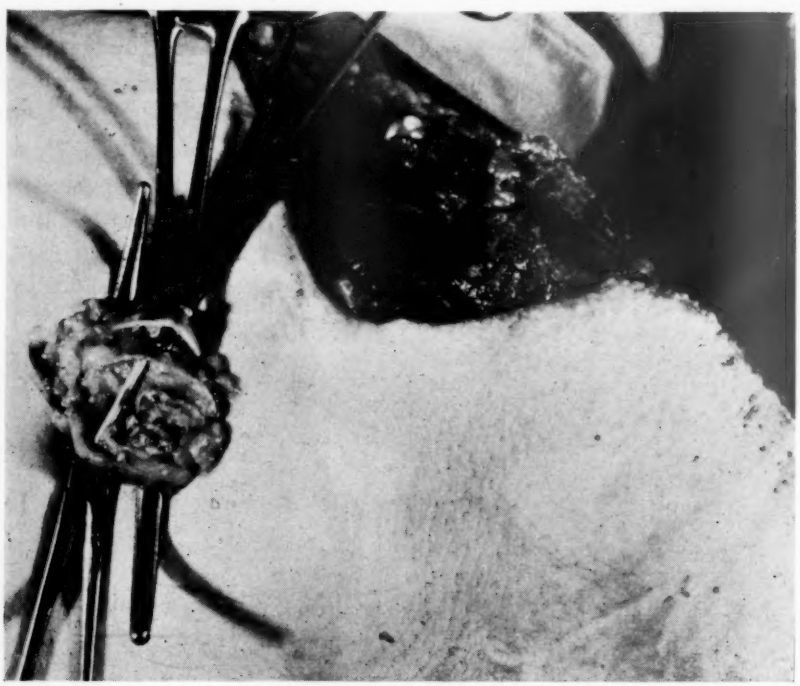

Fig. 4 (Case 1).—Clamps elevate only involved nodes in amputated quarter.

CASE 2.—J. T. J., a 35-year-old white man, was admitted to Kennedy Hospital, Sept. 17, 1948. He had noticed a small red sore on the anterior aspect of his right ankle for a period of two and one-half years. It progressively increased in size, was asymptomatic except for slight bleeding when it was injured. A local surgeon removed the lesion two weeks prior to admission and the pathologic study proved to be malignant melanoma. There was a healed incision just above the ankle and a pea-sized mass in the right femoral region. Metastatic survey was negative. Hemipelvectomy was performed Sept. 22, 1948. The wound healed per primam and he was discharged from the hospital on Nov. 1, 1948. Examination of the resected limb revealed involvement of the lymphatics deep to the muscles locally and one femoral node was involved in the malignant process. There was no enlargement of lymph nodes in the iliac region.

Follow-up Study.—Six months postoperatively there was no evidence of melanoma in the flap. There were no metastases.

CASE 3.—T. M. B., a 53-year-old white man, entered the hospital in January, 1948, for the treatment of a mass which had appeared in the left axilla, and rapidly grew to the size of a grapefruit. Four years previously he had had a mole removed from the posterior scapular region. The small scar from this healed incision was widely excised and microscopic study

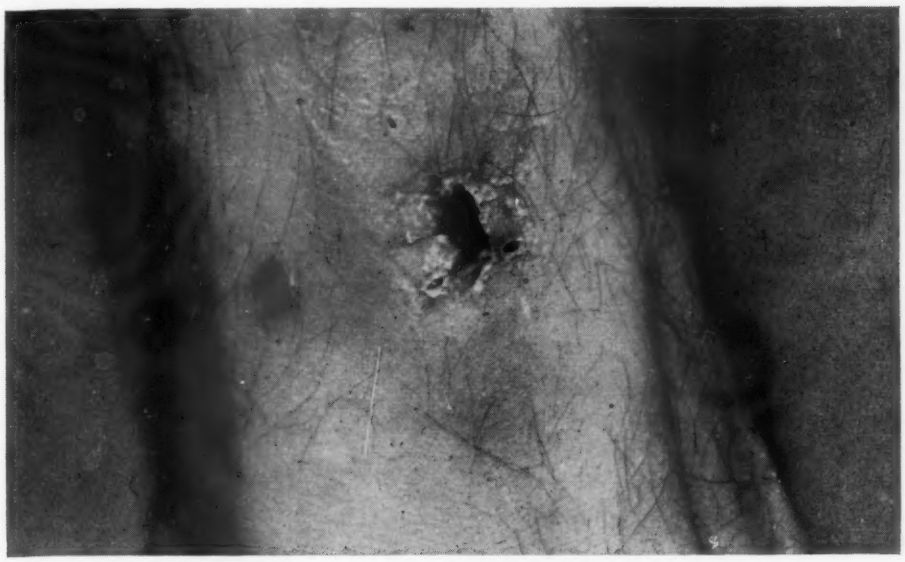

Fig. 5 (Case 2).—Local lesion just above ankle.

Fig. 6 (Case 2).—Arrow points to single involved node; iliac vein has been ligated approximately two inches above Poupart's ligament.

proved the presence of melanoma in the scar, although it was not possible to know this from clinical examination. Interscapular amputation of the left arm was performed Feb. 27, 1948, after a period of ineffectual radiation therapy had been done at the patient's request. The wound healed per primam and the patient was discharged March 12, 1948. He returned to the hospital in October, 1948, when an examination of the operative region showed it to be free of disease. There were several enlarged lymph nodes in the opposite side of the neck. Radical resection of the glands of the right neck and hemithyroidectomy were performed at this time. Study of the amputated member revealed a large conglomerate mass of axillary lymph nodes involved with melanoma. The neck dissection specimen included many lymph nodes with melanomatous involvement and the presence of the tumor in the right lobe of the thyroid. He was discharged on Nov. 8, 1948, with per primam healing in the neck incision, but returned promptly because of weakness in the right arm and hand, headache, nausea, and vomiting. Now nodules were observed in the scalp, left side of the neck, in the flaps of the amputation scar, chest, and abdomen. Cerebral metastases produced coma and he died Nov. 17, 1948—five years after the original mole excision, nine months after the interscapular amputation, and one month after the radical neck dissection. Autopsy showed widespread metastases to skin, brain, left cervical lymph nodes, and chest. The amputation flaps were clinically free from nodules until the final dissemination, but no more nodules were present in these flaps than in the scalp.

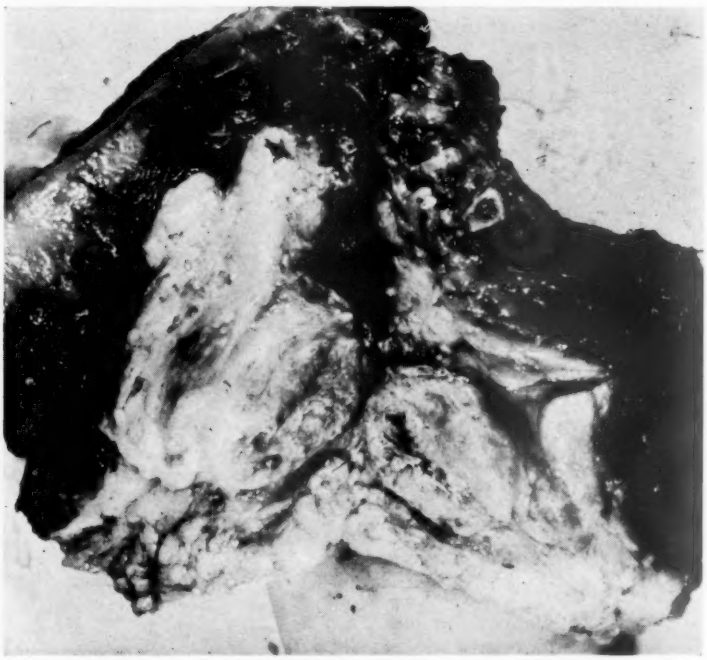

Fig. 7 (Case 3).—Interscapulothoracic amputation; large whitish areas show extensive involvement of nodes.

CASE 4.—T. M. R., a 59-year-old white man, had a mole near the right ankle, of one year's duration. The mole bled when struck six months prior to admission. There was a mass in the right groin two and one-half months before admission. Metastatic survey was negative. Positive biopsy was done by radical local excision. On Jan. 4, 1949, an anterior incision was made for proposed hemipelvectomy. When the iliac vessels were exposed, several large, firm, grayish lymph nodes were noticed. Involvement was suspected. Four glands were removed and operation was abandoned. Careful serial studies of the glands failed to show anything but infection. On Jan. 10, 1949, hemipelvectomy was performed. The wound healed per primam. Epididymitis due to catheter complicated his recovery. The resected limb

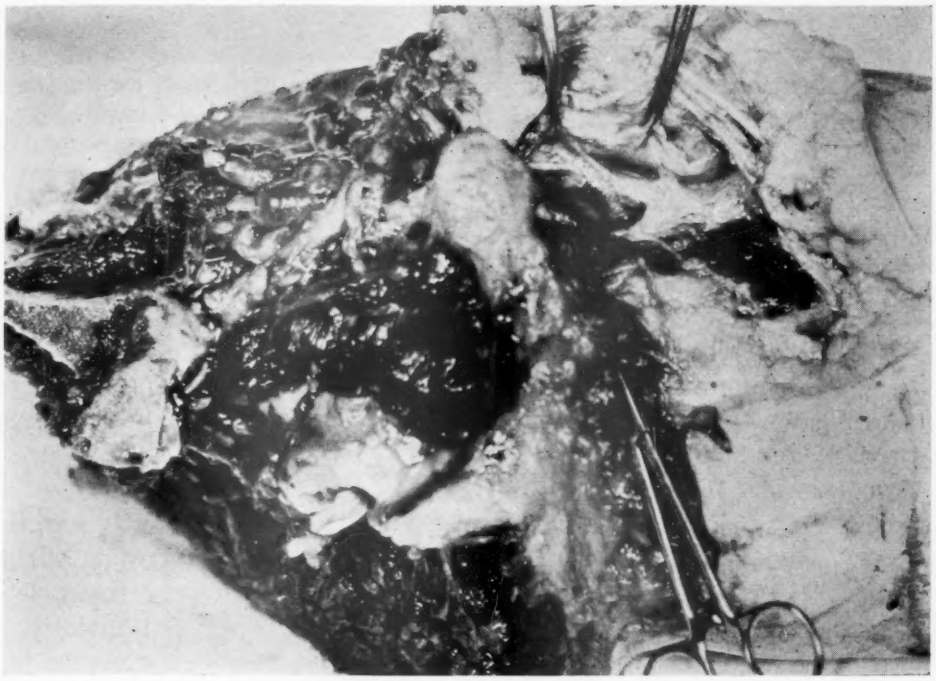

Fig. 8 (Case 4).—Extensive involvement of nodes in femoral region; enlarged nodes above Poupart's ligament show inflammation.

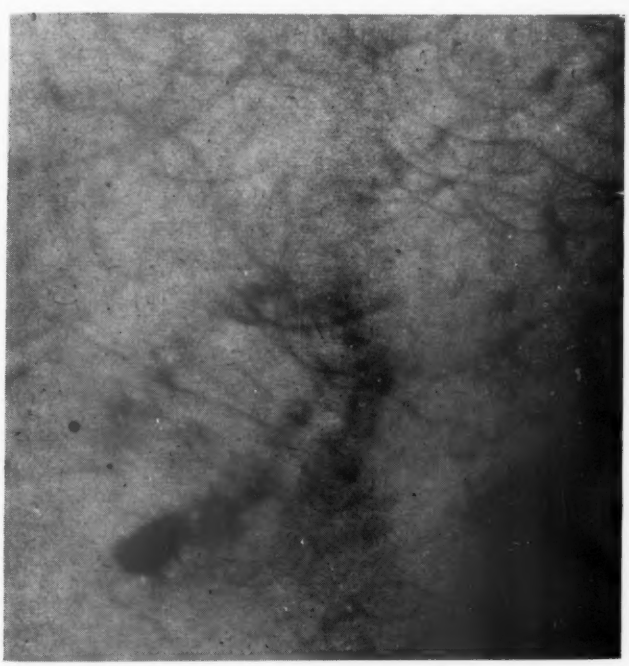

Fig. 9 (Case 5).—Local lesion on the calf; recurrent melanoma in scar two years after local removal. Quarterectomy not done in this case.

showed that biopsy excision had been total removal. There were many enlarged and involved femoral glands. Remaining iliac glands again failed to show the presence of melanoma.

CASE 5.—W. C. P., a 24-year-old white man, had a mole removed from the left mid-calf region two years before admission. On January 22 he noticed a small mass in the left femoral region while playing basketball. He consulted a physician who incised the gland and noticed the escape of blackish material from the glands. Sections revealed melanoma. He was admitted to Kennedy Hospital on Jan. 26, 1949. The local lesion consisted of a dime-sized scar on the left calf in which were small black areas, obviously melanoma. Hemipelvectomy was advised. The patient refused and left the hospital to find a surgeon who could treat the lesion successfully without amputation.

COMMENTS

These cases are believed to be examples of slow-growing melanoma. Case 4 may be more fulminating than the rest of the group and the sequence of events in the arm case suggests that after a four-year period, the tumor was now reaching the sudden dissemination stage.

Two patients (Cases 3 and 5) underwent local minor surgery for their malignant moles four and two years, respectively, before glandular metastases appeared. Both had melanomatous involvement of the scars when admitted to Kennedy Hospital. These findings suggest that local surgery, incomplete as it was, had no effect upon the ultimate fate of the tumor and that the long periods of time between local excision and metastases can be attributed to the natural slow growth of the neoplasm, rather than to triumphant success due to surgical excision. Also, it is suggested that the trauma of the local lesion in these two cases certainly did not contribute to metastatic involvement.

Case 2 demonstrates what may be false security when one relies upon "excision in continuity" operation because the lymphatics lying deep in the muscles of the calf contained melanoma cells. These lymphatics would not have been effectively removed by any operation short of ablation. The arm case demonstrates that with quarterectomy, spreading metastases in the skin flaps did not occur until subcutaneous nodular involvement appeared simultaneously in many other parts of the body. We had treated a similar case by radical axillary dissection. Three months following operation the patient returned to the hospital with widespread metastases of the skin flaps. This latter patient had refused interscapulothoracic amputation. In all of the amputated limbs, thorough search of the tissues failed to reveal the presence of melanoma above the femoral nodes. Case 4 demonstrates the difficulty in establishing this fact, and the simplicity with which it is solved. When the iliac nodes were noted to be suspiciously enlarged during the first operation, the anterior wound was closed and enough time was allowed for the pathologist to be certain of non-involvement before quarterectomy was accomplished six days later. Obviously, if involvement of nodes is present at the level of the hypogastric artery or above it, quarterectomy should not be performed, because proof is then at hand to establish its futility. It is doubtful that quarterectomy would be a fitting procedure for palliation alone. Finally, one is compelled to react favorably to the application of radical surgery in the arm case and the last leg case. If, instead of local excision which was done early in these cases, quarterectomy had

been done, one cannot escape the conclusion that not only five-year survival rates could be obtained in larger numbers of cases, but that there should be a fair number of permanent cures in the slow-growing cases. This concept must be true or we should abandon radical surgery for malignant tumors. It is an interesting observation to notice that experienced surgeons will vigorously maintain that the "most radical operation possible" should be performed in melanoma cases; yet when the actual working procedures of these same surgeons are surveyed, they do not include really radical surgery. In other words, we speak of it, but do not do it. Handley, Pringle, Pack, and a few others have come closer to it than others. In a recent consultation with a well-qualified surgeon concerning an early lesion on the heel, this surgeon was horrified when quarterectomy was suggested, but stated that he must do a tremendously radical operation locally, and he believes that he is doing a radical operation. However, when he and the pathologist were queried about prognosis, both unhesitantly and promptly remarked that the patient would die of melanoma. Herein lies the trouble. We cannot expect the public to accept quarterectomy unless the surgeons and pathologists are convinced of its worthiness. It also appears to be wasteful and pointless to continue to bombard the lay public with propaganda about early recognition of malignancy and prompt radical therapy in the early lesion, when we actually fail to apply this radical surgery early. Reference has been made earlier in this article to the fact that melanoma is not so hopeless when compared to some other malignant tumors. One major reason exists in the fact that the lesion can be early recognized to reside at the end of a limb, a site which permits the most favorable radical surgery. The patient will accept it when we can prove to him that the radical attack is a justifiable one; and that instead of talking about it, we should do it, and not abandon it until such an attack has been proved to be hopeless.

SUMMARY

1. Five cases of slow-growing melanoma are briefly described.

2. The gross findings indicate that quarterectomy is the only procedure which will permit an increase in longevity or possible chance for permanent cure—if done early.

3. The few cases which demonstrate longevity are probably due to the slow-growing nature of the tumor rather than successful outcomes resulting from the surgical procedures previously employed.

4. Three cases were treated by hemipelvectomy and one by interscapulothoracic amputation.

5. Follow-up studies will be necessary on a large number of cases before justification of these mutilating procedures is established.

6. If this type of operation should fail to increase longevity or produce some cures, it would then be suggested that surgery is not playing a significant role in the treatment of melanoma.

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STUDIES IN ACUTE CHOLECYSTITIS

I. Surgical Management and Results

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THE value of early surgical intervention in acute cholecystitis has been demonstrated by the excellent results reported by Heuer[1] and Glenn.[2] Surgery is indebted to them for their persistent advocation of what originally was a radical departure from accepted practice. At the Peter Bent Brigham Hospital the late Professor Elliott Cutler abandoned a policy of extreme conservatism in the treatment of acute cholecystitis in 1935. The advantages of early operation were recognized but because many patients entered the hospital in the late stages of the disease, it was felt that early operation in terms of the pathologic process was not always possible. Accordingly, a policy of individual management was outlined whereby an attempt was made to select the optimum time for surgery for each patient.[3] Under this plan of management, it was possible to carry out exploration of the common bile ducts in a large percentage of cases and at the same time reduce the mortality to the same levels reported by the advocates of prompt surgery in every case.[4]

The present report records the experience of the Peter Bent Brigham Hospital during the years 1941 to 1947, inclusive. The over-all experience with biliary surgery during this period is shown in Table I. It is gratifying to note that the operative mortality in acute cholecystitis is approaching that of elective surgery on the gall bladder and biliary passages.

The operative procedures employed in the 134 patients who came to surgery for acute cholecystitis are shown in Table II. There were 114 cholecystectomies, 50 of which were combined with exploration of the bile ducts, without a fatality. Twenty patients (15 per cent) had cholecystostomy performed and as 2 of these required a second cholecystostomy after a long interval of freedom from symptoms, these are considered as separate primary procedures. There were 2 deaths. In 12 cases, secondary operations were performed after preliminary cholecystostomy, the common duct being explored in 6 of these. There were no deaths in this group. The operative mortality of 1.5 per cent is computed in relation to the number of patients rather than the number of procedures.

In a study of acute cholecystitis the importance of recording all cases whether medical or surgical has been emphasized recently by Judd.[5] It is obvious that if apparently moribund patients are excluded from consideration, it is possible to present a favorable surgical mortality without giving a true picture of the disease. During the period of this study, there were 19 cases

Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 24-26, 1949.

TABLE I. BILIARY SURGERY*

	CASES	DEATHS	MORTALITY (PER CENT)
Cholelithiasis; chronic cholecystitis	515	4	0.8
Acute cholecystitis	134	2	1.5
Total	649	6	0.9

*Exclusive of cancer and strictures.

TABLE II. SURGERY IN ACUTE CHOLECYSTITIS

OPERATION	CASES	DEATHS
Primary		
Cholecystectomy	64	0
Cholecystectomy + C.D.	50	0
Cholecystostomy	22	2
Secondary		
Cholecystectomy	6	
Cholecystectomy + C.D.	6	
Total procedures	148	
Total patients	134	2 (1.5%)

of acute cholecystitis in which surgery was not performed. Fifteen patients either refused operation or insisted upon postponing it because of exigencies imposed by the war. In 2 cases surgery was not recommended. Two patients died. Thus, in the entire group of 153 patients there were 4 deaths, an over-all mortality of 2.6 per cent.

The age of the patients is shown in Table III. There were no operative deaths in patients under 78 years of age. The 2 patients who died without surgery were 65 and 66 years of age, respectively. All of the patients who died entered the hospital over four days after the onset of symptoms. Thus, there were no deaths at any age in patients who entered the hospital within forty-eight hours of the onset of symptoms.

TABLE III. AGE AND MORTALITY

DECADE	CASES	DEATHS
3rd	11	0
4th	16	0
5th	27	0
6th	37	0
7th	42	2
8th	18	2
9th	2	0
	153	4 (2.6%)

THE INDICATIONS FOR AND CHOICE OF OPERATION

The ideal treatment of acute cholecystitis is early cholecystectomy with exploration of the common bile duct as indicated. This should be the objective in every case regardless of the duration of the disease. Unfortunately, however, difficulty in establishing the diagnosis and the poor condition of many of the patients make the attainment of this ideal well-nigh impossible. In our experience a great variety of diseases, acute hepatitis, coronary occlusion, or disease of the right kidney, to mention a few, may simulate acute cholecystitis and vice versa. In these situations immediate operation can

hardly be regarded as the procedure of choice. In 26 instances in this series operation was delayed for over forty-eight hours because the diagnosis was obscure. It is noteworthy, however, that in only 4 of these cases had the patient entered the hospital within forty-eight hours of the onset of symptoms.

Assuming the diagnosis to be reasonably clear and considering only the condition of the patient, there are four possible courses for the surgeon to choose. The first is prompt definitive surgery as soon as fluid balance has been established; the second is an emergency cholecystostomy as a lifesaving procedure; the third is delay in hopes that by such delay the condition of the patient can be improved and the inflammatory process allowed to subside sufficiently to permit definitive surgery to be performed; the fourth and rarest choice is delay hoping that no operation will be necessary. Reasons for these decisions and the hazards involved are illustrated by our experiences.

The relation between the time of admission and the time of primary operation is shown in Table IV. Definitive surgery was carried out within forty-eight hours of admission in 49 patients, the common duct being explored in 30 per cent of them. One-half of this group had entered the hospital over forty-eight hours after the onset of symptoms. Although the classical clinical findings of acute cholecystitis were present and were confirmed pathologically, these patients were not gravely ill. Only 3 of them were jaundiced. The gall bladder was gangrenous in only 1 case and there was no instance of perforation or abscess formation. This is the ideal management of acute cholecystitis. Moreover, it is the condition of the patient rather than the mere duration of the disease which is the determining factor in the decision to operate. Finally, we do not regard this as an emergency procedure to be performed late at night or under unfavorable circumstances. If the patient is so ill that operation cannot be deferred a few hours, cholecystostomy is the procedure of choice.

TABLE IV. RELATION BETWEEN TIME OF ADMISSION AND PRIMARY OPERATIVE PROCEDURE

TIME OF OPERATION	TIME OF ADMISSION	
	UNDER 48 HR.	OVER 48 HR.
Early definitive (under 48 hr.)		
Cholecystectomy	15	18
Cholecystectomy + C.D.	10	6
Emergency cholecystostomy	14	6
Delayed definitive (over 48 hr.)		
Cholecystectomy	12	19
Cholecystectomy + C.D.	18	16
Late cholecystostomy	0	2
	69	67

Cholecystostomy was performed in 22 cases. Twenty of these were carried out within forty-eight hours of admission and in 16 cases the disease was of less than forty-eight hours' duration at the time the patient arrived at the hospital. In 5 cases cholecystostomy was required by technical difficulties encountered at operation but in the remaining cases it was a planned procedure performed through a small, muscle-splitting incision under local anesthesia. As a group these patients were by far the sickest in the series. All but 2 were over 50 years of age and 15 were over 60 years. Three were di-

abetic, 5 had advanced cardiovascular disease, and 3 were jaundiced. In 1 there was a large subhepatic abscess and in 3 there were perforations of the gall bladder. The 2 cases in which cholecystostomy was performed over forty-eight hours after admission require an explanation. One was a difficult diagnostic problem and the other was a patient, aged 78 years, with comparatively mild cholecystitis in whom it was at first thought operation could be avoided.

The value of cholecystostomy has been emphasized[2, 3, 6] many times but there is still a tendency to regard it as a compromise operation. We feel that it has a definite and permanent place in the surgeon's armamentarium. It is the procedure of choice in the toxic, elderly, or diabetic patient particularly if first seen in the more advanced stages of the disease. Properly executed under local anesthesia, cholecystostomy adds nothing to the gravity of the patient's condition and it is unquestionably lifesaving in a majority of these cases. It would probably remain the procedure of choice in 5 to 10 per cent of the cases even if all patients entered the hospital early in the disease.

Whether or not cholecystostomy is to be followed by definitive biliary surgery must be settled as an individual problem in each case. In general, it should be regarded as the first step of a two-stage procedure. Twelve, or two-thirds, of our patients who survived cholecystostomy had subsequent cholecystectomy and in 6 of these the common duct was explored. However, in the aged, debilitated, or poor-risk patient it may be best to postpone cholecystectomy indefinitely provided the patient remains asymptomatic. Under such circumsances a cholecystocholangiogram is done before the patient is discharged in order to demonstrate patency of the cystic duct and to exclude common duct stones.

In 8 of our cases no further surgery was advised after cholecystostomy. Four of these patients have remained asymptomatic for five years. In 2 no follow-up data are available. The remaining 2 patients returned to the hospital after intervals of six months and four years, respectively, with recurrent acute cholecystitis. One of these patients was 82 years old at the time of the first cholecystostomy. Six months later a second cholecystostomy was necessary but because of very advanced coronary artery disease with heart failure further surgery was again considered unwise. She remained comfortable and asymptomatic for eighteen months, eventually dying of coronary occlusion. The other patient was 74 years of age at the time of the first cholecystostomy. She lived comfortably for four years, then re-entered the hospital with another acute attack of cholecystitis and died of pulmonary embolism after a second cholecystostomy at the age of 78 years.

Definitive surgery was delayed for over forty-eight hours after admission to the hospital in 65 cases. Over one-half of these patients had entered the hospital forty-eight hours or more after admission. Difficulty in establishing the diagnosis and the general condition of the patients were the principal reasons for delay. These patients were not so ill that an emergency cholecystostomy was deemed necessary but, on the other hand, were not thought to be adequately prepared for operation particularly when exploration of the

common bile duct was contemplated. As might be expected, jaundice was present in 30 of the 65 cases.

If one elects to delay surgery, the details of management are of considerable importance. The progress of the disease as manifested by the temperature, pulse rate, laboratory data, symptoms, and local physical signs are evaluated at frequent intervals throughout the day and at night in doubtful cases. Fluid balance is established promptly by the parenteral rout but fluids and a high carbohydrate and high protein intake are given by mouth if there is no vomiting or distention. Penicillin and vitamin K are administered routinely in appropriate doses. Definite evidence of subsidence of the local inflammatory process and a general improvement in the condition of the patients is a requisite for continued observation. The precise indications for abandoning this course and resorting to cholecystostomy will be presented in another communication.

This plan of management is admittedly hazardous because of the dangers of perforation or abscess formation even when the clinical manifestations of the disease are subsiding. It is our belief, however, that by judicious delay the experienced surgeon is able to prepare many patients for definitive surgery including exploration of the common duct whereas by immediate operation he might be committed to a more limited operation. The morbidity and mortality occasioned by stones left in the common duct make choledochostomy a desirable objective. The fact that none of the patients in this group died and that common duct exploration was performed in one-half of the delayed operations encourages us in this stand.

On the other hand, although as a group the patients in whom surgery was delayed were not as ill as those in whom cholecystostomy was performed, there were many gravely ill patients among them. A critical review of these cases indicates that in several instances an emergency cholecystostomy might have been a wiser choice. Thus, 7 patients in this group had local abscesses by the time operation was performed. It is interesting, however, that in all of these cases definitive surgery was completed and that the postoperative course was uncomplicated.

In many instances surgery was postponed for an unduly long time, thus greatly increasing the morbidity. In this connection the time at which surgery was done in relation to the onset of symptoms is interesting (Table V). It can be seen that over 50 per cent of the operations were performed between the second and twelfth day, a time which many surgeons consider to be a period in which surgery is contraindicated. Reluctance on the part of many of our staff to operate during this period is reflected by the group of 48 patients who were operated upon after the twelfth day. In reviewing these cases it is our feeling that little was gained by the prolonged delay and that frequently the technical procedure was rendered more difficult by the development of dense scar tissue in and around the gall bladder. A clinical and pathologic study of this material which will be presented more fully as a separate communication has convinced us that acute inflammation of the gall bladder does not resolve as is the case with the appendix. Once damaged by acute inflamma-

tion, the gall bladder undergoes a slow and progressive fibrosis which makes surgery increasingly difficult with the passage of time. The reason for postponing surgery, therefore, is to improve the general condition of the patient so as to permit a definitive operation to be performed, rather than to allow complete resolution of the local inflammatory process. Prolonged delay because of persistent evidence of local inflammation is unwarranted and unprofitable. In our experience it was under such circumstances that local perforations and abscesses developed. Moreover, there must be no gambling in the management of this admittedly controversial group of cases. If there is the slightest doubt about the progress of the case, cholecystostomy should be performed.

TABLE V. DURATION OF DISEASE FROM ONSET TO OPERATION

DAYS	CHOLECYSTECTOMY	CHOLECYSTECTOMY + C.D.	CHOLECYSTOSTOMY	TOTAL
0-2	11	4	2	17
2-4	11	7	9	27
4-12	19	16	9	44
12+	23	23	2	48

The rarest decision which the surgeon is called upon to make is to withhold operation in the hope that no surgery will be necessary. The hazards of nonsurgical management of acute cholecystitis are fully appreciated, but it is our considered opinion that here again the principle of individualization applies. In exceptional cases the best interests of the patient are served by conservative management. On three occasions in this series this course was elected. One was a woman of 78 years with a recurrent attack after a previous cholecystostomy. This case is described in detail later (Case 4). The other two patients were over 60 years of age and both were enormously obese. One had advanced cardiovascular disease and the other had had a recent abdominoperineal resection for cancer of the rectum with metastases. In both of those instances the cholecystitis subsided promptly and the patients have been asymptomatic for periods of two and three years, respectively.

THE INCIDENCE OF COMMON DUCT STONES

The frequency of common duct stones in acute cholecystitis has a direct bearing on the problem particularly if one accepts the principle of delaying operation in the hope of being able to carry out exploration of the bile ducts. In the 134 operative cases in this series the common duct was explored in 56 (42 per cent) (Table VI). In 50 of these the exploration was carried out at the primary operation and in 6 it was done at a second stage following earlier cholecystostomy. Common duct stones were recovered in 50 per cent of the cases explored or 21 per cent of the total number of operative cases. There were no operative deaths. However, in 2 cases in which surgery was not performed, common duct stones were found at autopsy. In this particular series the incidence of common duct stones may be fortuitously high but since the policy of individual management was instituted in this hospital in 1935,

common duct stones have been found in association with acute cholecystitis in 17 per cent of the cases. This high yield of common duct stones constitutes one of the strongest arguments in favor of the policy of individual management.

TABLE VI. INCIDENCE OF COMMON DUCT STONES IN 148 OPERATIONS ON 134 PATIENTS

	CD EXPLORED	STONES REMOVED	DEATHS
Primary operation	50	26	0
Secondary operation	6	2	0
	56	28	0
Ducts explored, 42% of patients			
Stones removed, 21% of patients			

The incidence of jaundice in association with common duct stones is of interest. In the entire series jaundice was encountered 37 times. Thirty-three of these patients had common duct explorations, stones being found in 25. There were 4 jaundiced patients in which the common duct was not explored. Two of these had cholecystostomies only, 1 had a cholecystectomy with aspiration of the bile duct, and in 1 no operation was performed but common duct stones were demonstrated at autopsy. In the 8 jaundiced patients in whom negative explorations were performed the degree of jaundice was slight, the icteric index being below 30. Postoperative cholangiograms revealed no calculi. This lends support to the belief that jaundice may occur in acute cholecystitis without stones in the bile ducts. However, until more reliable methods of detecting common duct stones prior to operation become available, jaundice must be considered a principal indication for choledochostomy.

In the absence of jaundice or a history of jaundice, common duct stones were found in 4 cases; 3 times in 23 surgical explorations of the bile ducts and once at autopsy. The large number of negative explorations which were required to avoid overlooking a few stones indicates the need for better methods of demonstrating common duct pathology prior to operation.

DEATHS

The four deaths in this series merit a brief presentation.

CASE 1.—A woman, aged 65 years, entered the hospital on the fifth day of her illness with generalized peritonitis. She had had no previous symptoms of gall bladder disease. The diagnosis of acute cholecystitis was completely missed and was established only at post-mortem. The patient was thought to have advanced mesenteric thrombosis and no operation was advised. Jaundice appeared terminally. Post-mortem revealed multiple stones in the gall bladder and common bile ducts, perforation of the gall bladder, and generalized peritonitis.

CASE 2.—A man, aged 66 years, entered the hospital on the tenth day of his illness with generalized peritonitis, a large pelvic abscess, and left lower lobe pneumonia. He had been under treatment for advanced pulmonary disease, thought to be tuberculosis. Although he was known to have gall stones and had had a previous attack of acute cholecystitis, it was thought that the pulmonary disease contraindicated surgery. Despite the previous history of gall stones this patient was thought to have perforation of the colon from carcinoma or diverticulitis. He rapidly deteriorated despite supportive measures. Autopsy revealed a perforated empyema of the gall bladder with a single, large stone in the gall bladder and thick sludge in the common duct. There was a generalized peritonitis, a large pelvic abscess, left lower lobe pneumonia, and extensive pneumonoconiosis.

CASE 3.—A man, aged 79 years, entered the hospital on the tenth day of his illness. He had had no previous symptoms of gall bladder disease. A diagnosis of perforated appendicitis was made and immediate operation performed under general anesthesia. A cholecystostomy was done when the true nature of the disease was recognized. This patient developed a Welch bacillus septicemia and died of generalized sepsis on the twenty-second day after operation. Autopsy was refused.

CASE 4.—A woman, aged 78 years, who had had a cholecystostomy performed four years before for acute cholecystitis entered the hospital on the fifth day of a recurrent attack. She had been quite well in the interim and did not appear seriously ill. Operation was delayed in the hope that the condition would subside spontaneously. Because of persistence of the attack a cholecystostomy was done on the third hospital day. The patient made an excellent, immediate recovery but died suddenly on the fourteenth postoperative day. Autopsy revealed massive pulmonary embolism. There was a single small stone remaining in the gall bladder. No stones were found in the common duct.

These 4 deaths can hardly be ascribed to the policy of individual management. However, they amply testify to the gravity of the disease and clearly indicate the necessity for early hospitalization. Moreover, 3 of them demonstrate the difficulties in diagnosis which may be encountered. Certainly in 3 of the cases earlier hospitalization might have led to a happier outcome by permitting a correct diagnosis to be made in which case emergency cholecystostomy might have been lifesaving. In Case 4 it might be arguel that had a cholecystectomy been performed four years previously after the initial cholecystostomy a more favorable outcome would have been assured. But if the patient had died of pulmonary embolism after an elective cholecystectomy, would there not be more grounds for criticism than under the actual circumstances?

CONCLUSIONS

The ideal management of acute cholecystitis is early operation with removal of the gall bladder and exploration of the common bile duct as indicated. In approximately 50 per cent of the cases delay in hospitalization, difficulty in making the diagnosis, and the poor general condition of the patients make this too dangerous. Under such circumstances one is faced with the choice of a two-stage operation, namely, emergency cholecystostomy to be followed later by cholecystectomy or delay in the hope of preparing the patient for a definitive single-stage operation. The incidence of common duct stones in acute cholecystitis is sufficiently high so that choledochostomy must be an objective in approximately 35 per cent of the cases. None of the deaths in this series are attributable to this plan of management. However, the principal error in this series was a tendency to delay operation too long a time, thus greatly lengthening the morbidity and in many instances increasing the technical difficulties of the operation by allowing dense scare tissue to develop in and around the gall bladder. The precise indications for cholecystostomy, the optimum time for delayed surgery, and the indications for choledochostomy require further study.

SUMMARY

The experience of the Peter Bent Brigham Hospital with acute cholecystitis during the period 1941 to 1947 is reviewed. The mortality including

operative and nonoperative cases was 2.6 per cent. The operative mortality was 1.5 per cent. Common duct stones were removed in 21 per cent of the operative cases without a fatality. All of the deaths occurred in patients over 65 years of age who entered the hospital over four days after the onset of symptoms.

The advisability of varying the management of this disease to fit the requirement of the individual patient is reaffirmed. The indications and time of election for surgery are discussed.

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AN EXPERIMENTAL STUDY OF THE EFFECT OF HEPARIN ON THE LOCAL PATHOLOGY OF BURNS

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IT IS a common clinical observation that the appearance of a burn when first examined does not give an accurate estimate of its final depth at the time the slough of necrotic tissue finally occurs. Leach and co-workers[2] and Moritz and Henriques[3] have shown that the destruction of epithelium and dermis is directly related to the temperature of the thermal agent and the duration of its application. Associated with this initial insult to the skin, there is a variable depth to which the endothelium of the superficial vessels is damaged. Further, sludging of blood in these vessels and those of deeper layers, destruction of the red and white blood cells by heat, and occasional thrombosis are also seen. With such vascular pathology existing in direct continuity with the deeper vessels of the dermis and subcutaneous fat, might there not occur an extension of actual thrombosis into the vessels of the deeper, but undestroyed, layers of the dermis and subcutaneous tissues?

It was our purpose in this work to study the vascular changes associated with the application of a thermal agent and the progression of these in control and heparinized dogs for a period of seventeen days. We hoped to be able to determine, by a study of sufficient duration, whether the entire loss of tissue resulted from the momentary application of the thermal agent or whether secondary vascular changes were instituted at the same time which would involve later the subjacent vascular channels in such a way as to cause further tissue necrosis or at least delay the reparative processes normally operative. At the same time that the study was carried out to ascertain the foregoing information, it was felt of interest also to determine whether application of anticoagulant therapy (heparin) might influence such vascular changes as did occur. Hughes and Dann,[1] Moritz,[4] and Underhill and co-workers[6] did not find that thrombosis secondary to thermal injury was of any frequency or importance. Pack,[5] however, reported that a predisposition to thrombosis exists because of the white blood cell disintegration, venous stasis, and the viscosity of blood in the damaged area following burning. He recorded the presence of fibrin thrombi and thrombi from precipitation. The results of our study agree more closely with those of Moritz and others in this regard. A study of these normal reparative processes following thermal damage to the epidermis and dermis, when compared to the speed and effectiveness of these same mechanisms with the addition of heparin therapy, has led to some additional and interesting observations which may have clinical therapeutic significance.

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Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 24-26, 1949.

METHOD AND MATERIALS

The burns in this study were obtained by applying, under intravenous pentobarbital sodium anesthesia, heated uniform steel blocks measuring ½ by ½ by 1 inch and weighing 32 grams to the dry, freshly shaved skin of dogs' backs. The blocks were heated in a muffle furnace at 100° C. for fifteen minutes prior to application, removed from the furnace singly, and placed end on to the dogs' skin for fifteen seconds, with the only pressure being the weight of the block itself. Moritz and Henriques[3] have demonstrated that any temperature over 70° C. for longer than one second would produce transepidermal necrosis. This temperature and time were evolved after some experimentation to reproduce the frequent human deep dermal burn and resulted in burns that included 40 to 100 per cent of the dermis.

A series of ten dogs was burned by this method. However, as considerable variation was encountered, a second group of six dogs was burned by heating the blocks in boiling water for thirty minutes and applying them to the skin for fifteen seconds as described. These blocks dried in two to three seconds after removal from the boiling water.

Each of these sixteen adult mongrel dogs was given six one-half inch square burns on one side of the back. Care was taken not to place the block over an underlying bony prominence. Using sterile technique, these burns were excised, by elliptical incisions in the normal periphery, under intravenous pentobarbital sodium anesthesia, four, twelve, twenty-four, thirty-six, forty-eight, and seventy-two hours later from eight of the animals and five, seven, nine, eleven, fourteen, and seventeen days later from the other eight. The wounds were closed primarily in two layers with interrupted silk and the excised tissue fixed immediately in 10 per cent formalin. As each animal was completed, it was reburned in an identical fashion in comparable locations on the opposite side of the back and the burns were removed exactly as before. This time, however, the animals were heparinized two hours after the burning. Thus each dog served as his own control. Each dog's burns varied considerably from those of the other dogs, depending upon the complexion, quality of the hair, and thickness of the skin. The burns in a given animal were roughly comparable.

Two hours were permitted to elapse prior to administration of heparin, for it was felt that such a time period would correspond roughly to the delay before a patient could reach such definitive care. Sodium heparin* (1 mg. per kilogram of body weight) was administered intravenously to obtain immediate effect, simultaneously with heparin in Pitkin's menstruum (10 mg. per kilogram of body weight) subcutaneously. The usual 5 mg. per kilogram dosage for human beings had to be increased to this level before effective levels were maintained for twenty-four to thirty-six hours. A clotting time of more than twenty minutes was maintained throughout the remainder of the experiment by repeated injection of heparin in Pitkin's menstruum. The three-tube Lee-White method of clotting time determination was used. No

*Sodium heparin was supplied through the courtesy of The Upjohn Co., Kalamazoo, Mich.

complications to heparin were encountered other than one large hematoma occurring subcutaneously twenty-four hours after excision of a burn.

RESULTS

The repair mechanisms following injury to the epidermis and dermis by a thermal agent are very interesting and efficient. They follow a fairly definite and consistent pattern; namely, infiltration of polymorphonuclear leucocytes into the junction of destroyed and unburned skin, which leads finally to separation of this slough as an eschar of dead tissue; vascular regeneration, with new growth of capillaries from the uninjured tissue up to this junction accompanied by fibroblastic proliferation. This serves the function of a scaffolding on which epithelial regrowth may take place and at the same time carries nutrition to the newly formed epithelium.

With all of these mechanisms normally operative, healing will proceed to completion if first, the burn is small enough so that regrowth from the edges of normal skin may cover the entire injured area or, second, if the depth of the burn was insufficient to destroy all of the hair follicle epithelium in the lower dermis and subcutaneous tissue. In the latter the regrowth of epithelium will take place from these retained, undamaged epithelial rests in the base of the burn. Lastly, if the burn is too large for complete coverage by these, then this same mechanism will produce a layer of granulation tissue, the surface of which is formed by a layer of fibroblastic tissue containing a very rich vascular network of normal capillaries. This makes an ideal bed on which a skin graft may be expected to grow.

Our study corroborates the findings of Hughes and Dann,[1] which indicated the primary importance of vascular supply and regeneration in the healing process of a burned tissue. It serves to carry to the zone of junction, between the destroyed and normal skin, the "shock-troops" which must clean up the debris from the primary attack; namely, the polymorphonuclear leucocytes. It is also the source by which nutrition can reach the newly formed connective tissue and must precede the regrowth of epithelium from the edge or from the base.

Vascular Changes.—Hughes and Dann[1] state that burns are usually fully vascularized by the twelfth to sixteenth day, depending on the size of the burn. Vascularization precedes both epithelialization and fibroplasia in the superficial part of the burn, while in the deeper tissues the formation of new capillaries and fibroblastic proliferation seem to proceed hand in hand. Approach to the surface of the new dermis is upward between the fascicles of undestroyed dermal collagen.

This study of the vascular changes following deep burns was directed to four areas: (1) the zone in the dermis between the destroyed and normal or unburned dermis, (2) the blood vessels in the subcutaneous fat layer and the hypodermis of Moritz, (3) from the normal tissue at the periphery of the excised burn, and (4) the vessels in the platysma muscle and subjacent to it.

At junction of the destroyed and viable dermis: The capillaries of the normal dermis are not obviously profuse and are most prominent in the papillae

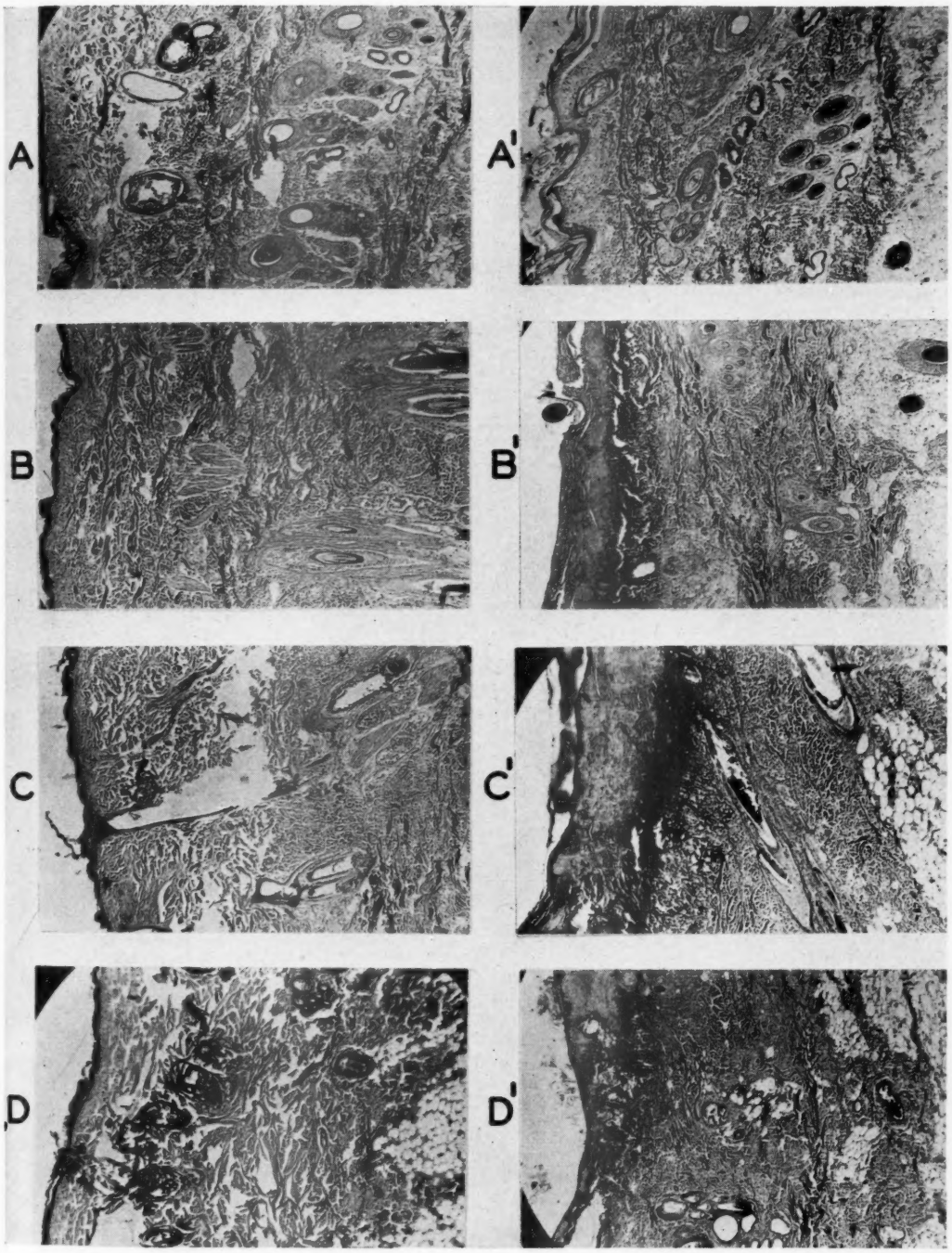


Fig. 1.—Photomicrographs of the full thickness of epidermis and dermis of burns removed from Dog 6 at *A*, twelve hours; *B*, thirty-six hours; *C*, seventy-two hours; *D*, five days without heparin. *A'-D'*, Same intervals during heparin therapy. (×45.)

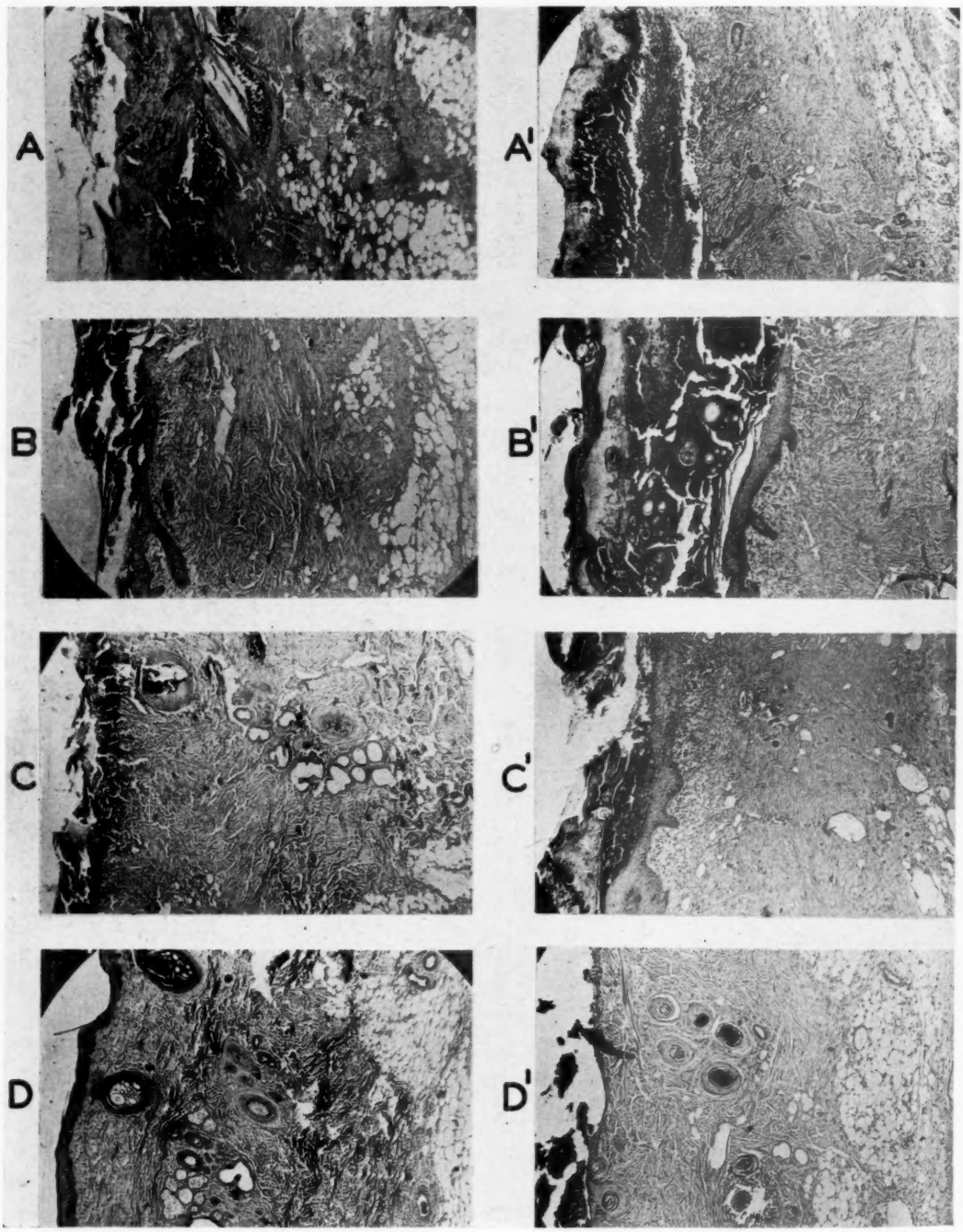


Fig. 2.—Photomicrographs of the epidermis and dermis of burns removed from Dog 10 at *A*, nine days; *B*, eleven days; *C*, fourteen days; *D*, seventeen days. *A'-D'*, Same intervals during heparin therapy. (×45.)

of the dermis. Normally, following visible separation between the dying and viable dermis, there appears an increased number of capillaries which early, following a burn, seem to be old capillaries. By the thirty-six hour period, these capillaries in the controls may be empty or packed with sludged, abnormal red cells (Fig. 3, *A*). In the heparinized animals, by this same time, the sludging, that was also seen in them initially, has largely disappeared and capillaries are seen containing normal red cells which seem to be in a normally circulating vascular network (Fig. 3, *A'*). This same difference is still apparent in the seventy-two hour burn (Fig. 5, *A* and *A'*) but is not common after this period. An auxiliary evidence of normal circulation in this layer is the appearance, usually at thirty-six hours, of increased polymorphonuclear leucocytes in these capillaries of the heparinized animal. This occurs at seventy-two hours or later in the majority of control animals. Increased numbers of capillaries at this zone appear at forty-eight to seventy-two hours quite prominently in the heparinized animals and is just beginning at three to five days in the controls.

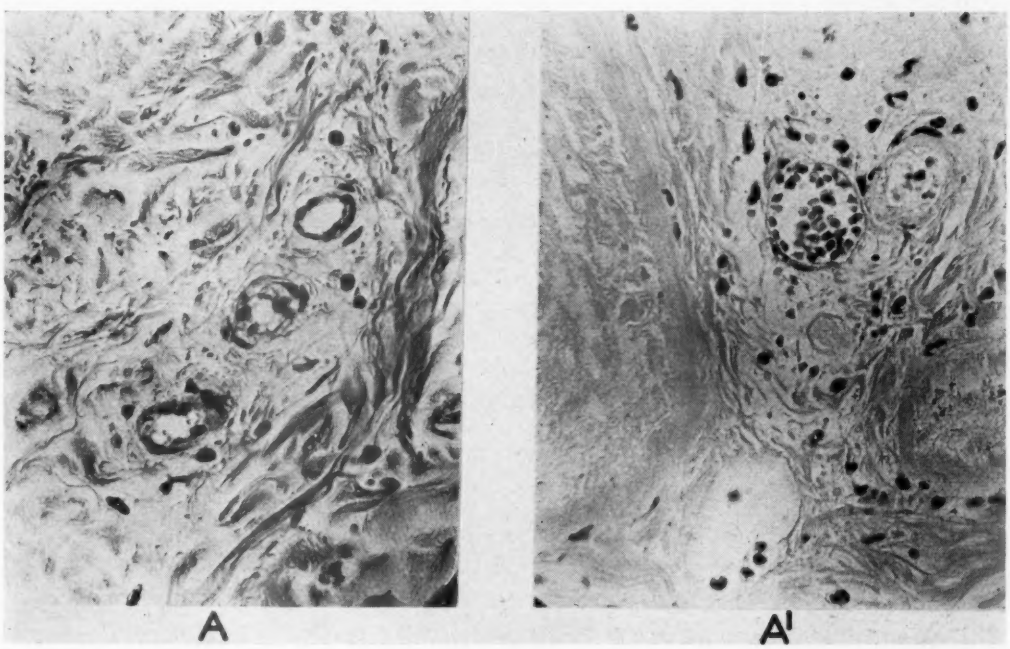


Fig. 3.—Photomicrographs (Dog. 6). Capillaries at junction between viable and nonviable dermis. *A*, At thirty-six hours without heparin; *A'*, with heparin. (×400.)

In the subcutaneous fat layer: The large and small arteries in this zone tend to be normal throughout the entire experiment. At four and twelve hours following the burn there is some evidence that they are less full than normal. As time progresses they quickly return to normal filling and continue so from the forty-eight to seventy-two hour period on in both groups. (Figs. 3 and 6.) The large and small veins in this same area early are more full than normal and in both series of experimental animals show sludging and abnormal red blood cells present up to thirty-six hours. Sludging first appears in both groups at the first examination, four hours following the burn. In general, the sludging in the heparinized animals is largely gone by the thirty-six hour examination and

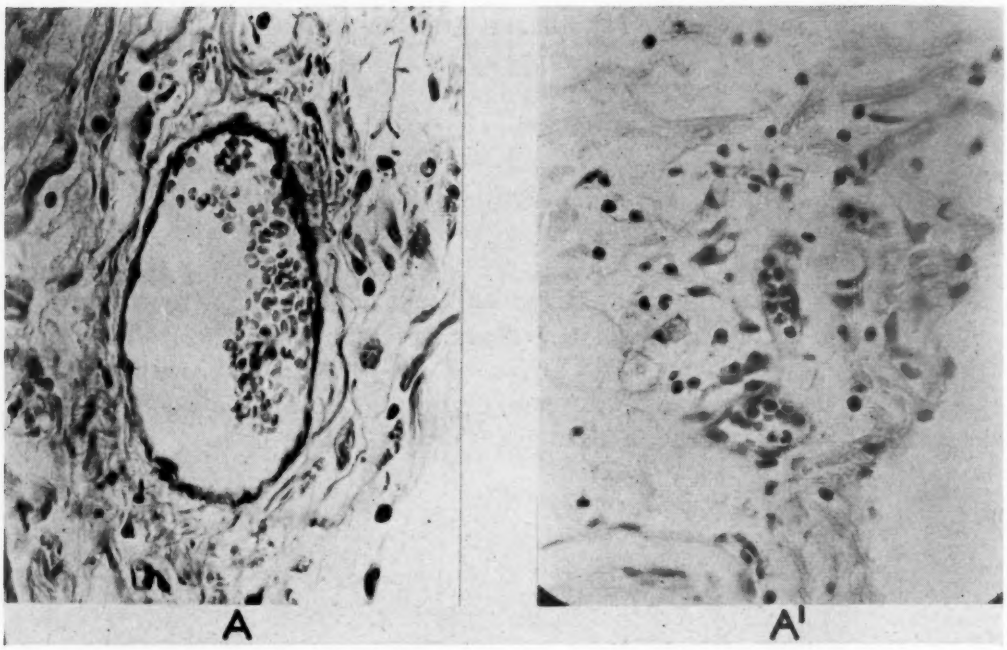


Fig. 4.—Photomicrographs (Dog 6) of veins in subcutaneous fat layer, subjacent to Fig. 3. *A*, At thirty-six hours without heparin; *A'*, with heparin. (×400.)

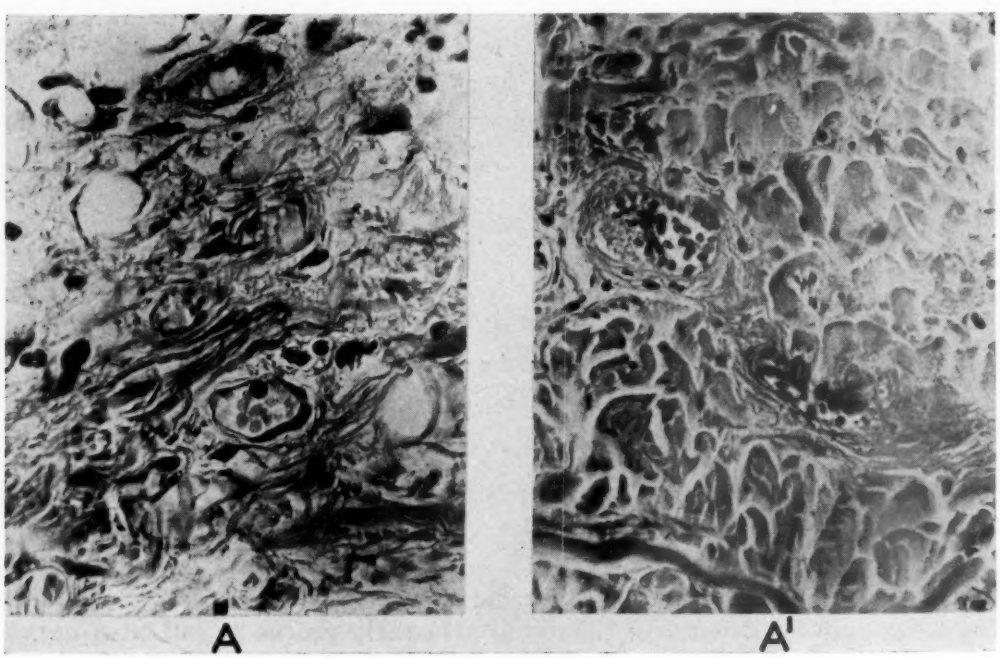


Fig. 5.—Same as Fig. 3 at seventy-two hours. (×400.)

no further evidence of abnormal red cells is found (Fig. 4, *A* and *A'*). In the control animals, this same change occurs at approximately seventy-two hours (Fig. 6). However, increased distention and sludging in the veins are still seen in many of the control animals up until the fifth day. As further evidence of normal circulation, polymorphonuclear leucocytes begin to appear in the arteries and veins at approximately twelve hours in the heparinized series and not comparably in the controls until thirty-six hours have passed. By the fifth to seventh day, all evidence of abnormal vascular arterial supply and venous return has disappeared in both experimental groups.

In general, therefore, the heparinized animals give evidence of being twenty-four to forty-eight hours ahead of the control series during the first three days of the examination as pertains to functional blood supply.

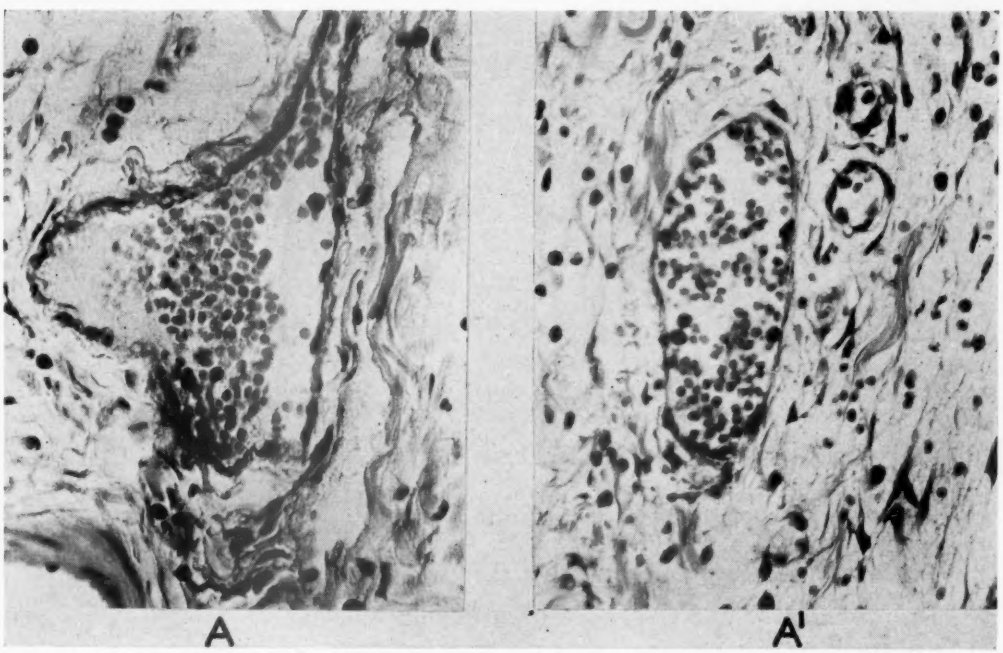


Fig. 6.—Same as Fig. 4 at seventy-two hours. (×400.)

In unburned tissue from the periphery: In general, sludging appears at the same time as mentioned in the subcutaneous fat tissue. It disappears a little more slowly here, in the controls, but at the same time in the heparinized series as mentioned previously. The appearance of polymorphonuclear leucocytes in these vessels very closely coincides with their arrival in the subcutaneous layer, as does the disappearance of abnormal red cells.

In the platysma muscle and subjacent to it: The characteristic changes in the blood supply in the areas above are somewhat similar here. However, the sludging appears at a later time, twelve hours in both heparinized and non-heparinized animals, but has disappeared by the thirty-six hour period in the heparinized and by three to five days in the control animals. The disappearance of abnormal red cells and the appearance of polymorphonuclear leucocytes closely coincides with the previous layers mentioned.

One other vascular change of interest, in comparing the two series of animals, is the capillary regeneration in the dermis and in the subcutaneous fat tissue. In the control animals, active capillary regeneration in the dermis begins at approximately nine days and seems to reach a point around the ninth day that is first reached by the heparinized animal at five days (Figs. 11, *A'*, and 12, *A*). Capillary regeneration in the fat begins first in the heparinized animals at the third day (Fig. 10, *A'*), is marked by the fifth day (Fig. 11, *A'*), and reaches a point at this time which is not usually reached before the ninth day in the controls (Fig. 12, *A*).

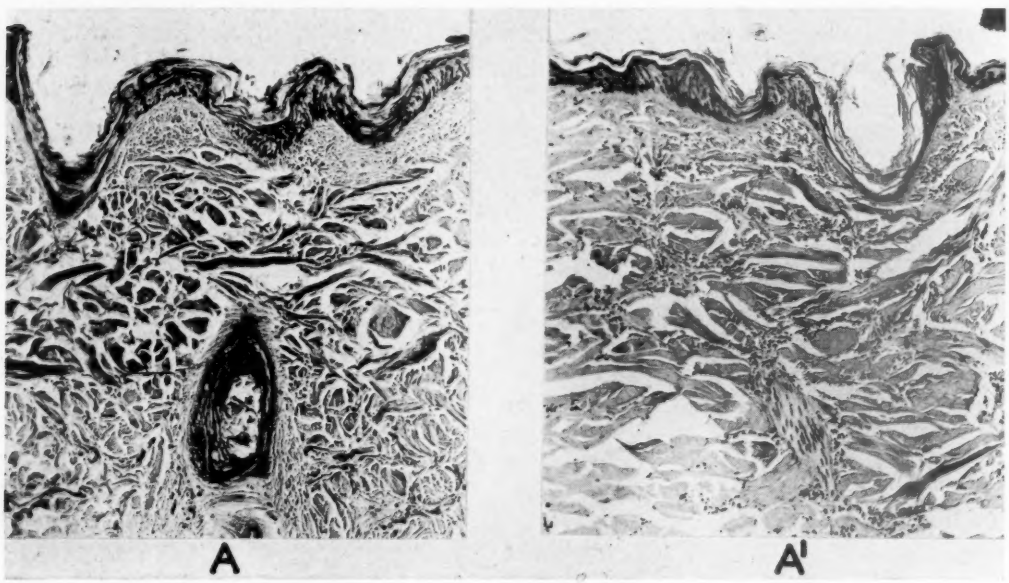


Fig. 7.—Photomicrographs (Dog 6) of polymorphonuclear infiltration in the dermis. *A*, At thirty-six hours without heparin; *A'*, with heparin. (×100.)

Infiltration of Polymorphonuclear Leucocytes.—

Into the dermis and the junction of viable and nonviable dermis: Polymorphonuclear infiltration into the areas of the junction of viable and nonviable dermis in the heparinized animals is usually seen to begin around twenty-four hours and is widespread by thirty-six hours (Fig. 7, *A'*) and generally reaches a comparable point in the control animals at seventy-two hours (Fig. 9, *A*). Fig. 9, *A* and *A'*, also shows the most common difference between the two groups of animals and demonstrates that by seventy-two hours in the heparinized animal a well-defined zone of demarcation has occurred between the viable and nonviable dermis. In general, the maximum infiltration occurs by the ninth day in the heparinized animals (Fig. 2, *A'*) and at eleven or fourteen days (Fig. 2, *B* and *C*) in the controls.

Into the subcutaneous fat layer: In general, the infiltration begins earlier in both series of animals in this layer than in the dermis. It is quite prominent by twelve hours in the heparinized series and by thirty-six hours (Fig. 8, *A'*) has reached a point which is roughly comparable with that generally seen in the

control animals at seventy-two hours (Fig. 10, *A*). During the third to seventh days following the burn, infiltration here gradually recedes as that into the dermis reaches its maximum. This decrease is coincident with the beginning of capillary regeneration and fibroplasia in the layer where the subcutaneous fat is immediately subjacent to the dermis.

This mechanism of polymorphonuclear infiltration operates eventually to produce a marked separation of this sloughed tissue from the underlying granu-

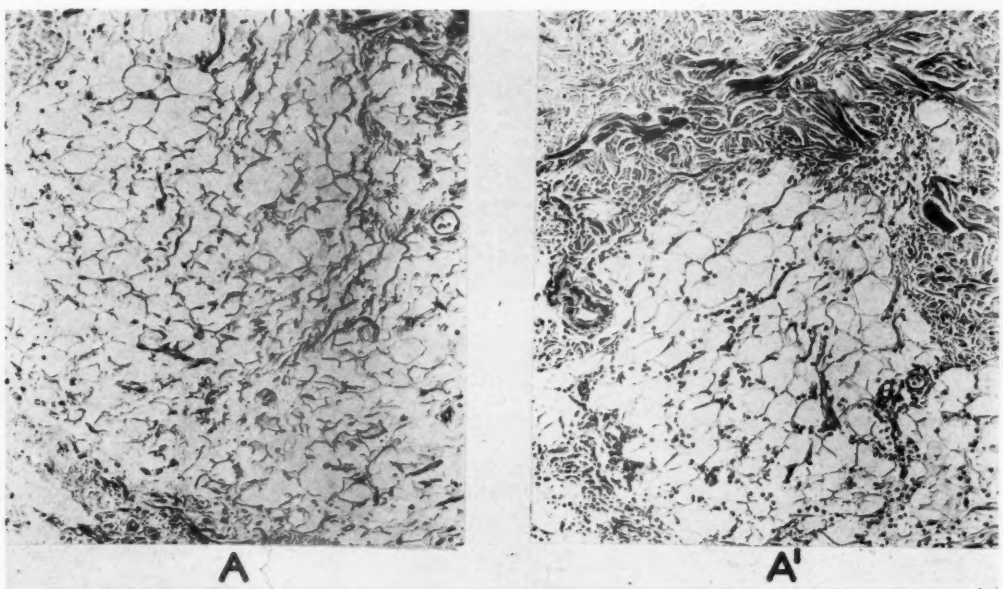


Fig. 8.—Same as Fig. 7 and subjacent to it in the subcutaneous fat layer. (×100.)

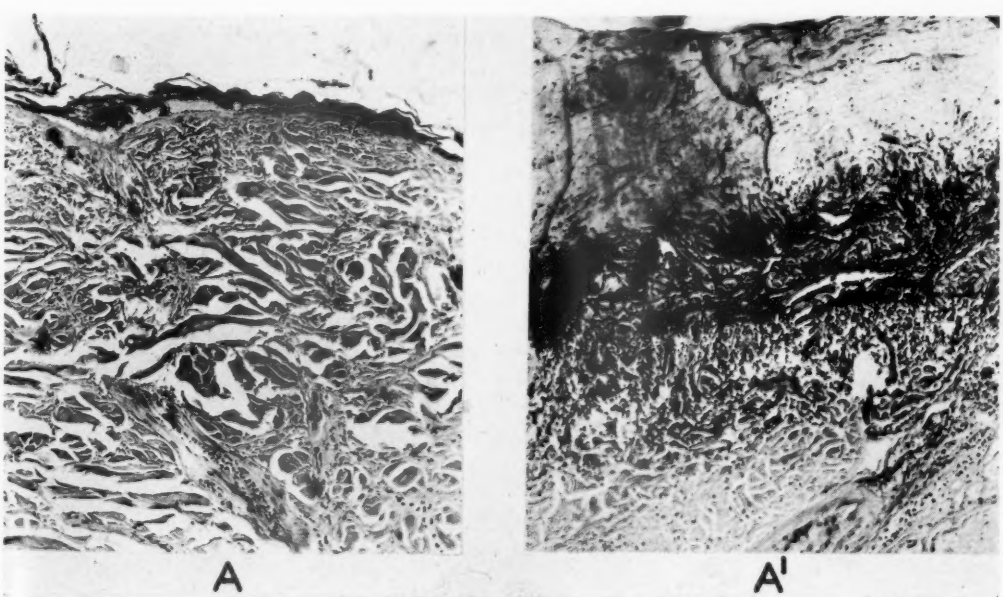


Fig. 9.—Same as Fig. 7 at seventy-two hours. (×100.)

lation tissue. This seems to reach a maximum in the nine-day heparinized series and in the fourteen-day control series in general. It is not infrequently seen that a burn may reach the point of complete healing when it is still covered by slough (Figs. 2, *D'*, and 13, *A*).

Fibroplasia and Regeneration of Dermis.—

In the hypodermis: The layer immediately subjacent to the dermis where it joints the subcutaneous fat tissue, called the hypodermis by Moritz, seems to

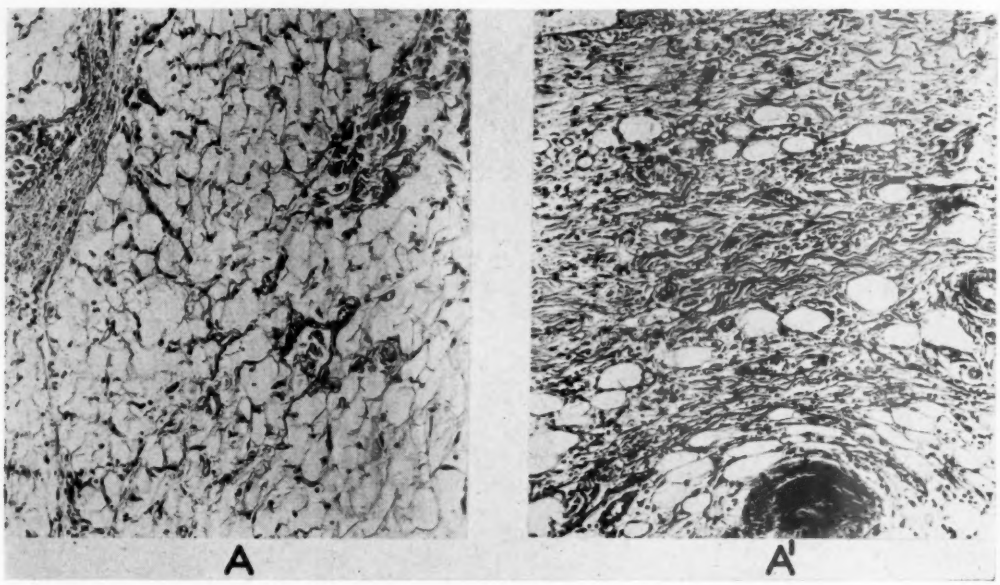


Fig. 10.—Same as Fig. 8 at seventy-two hours. (×100.)

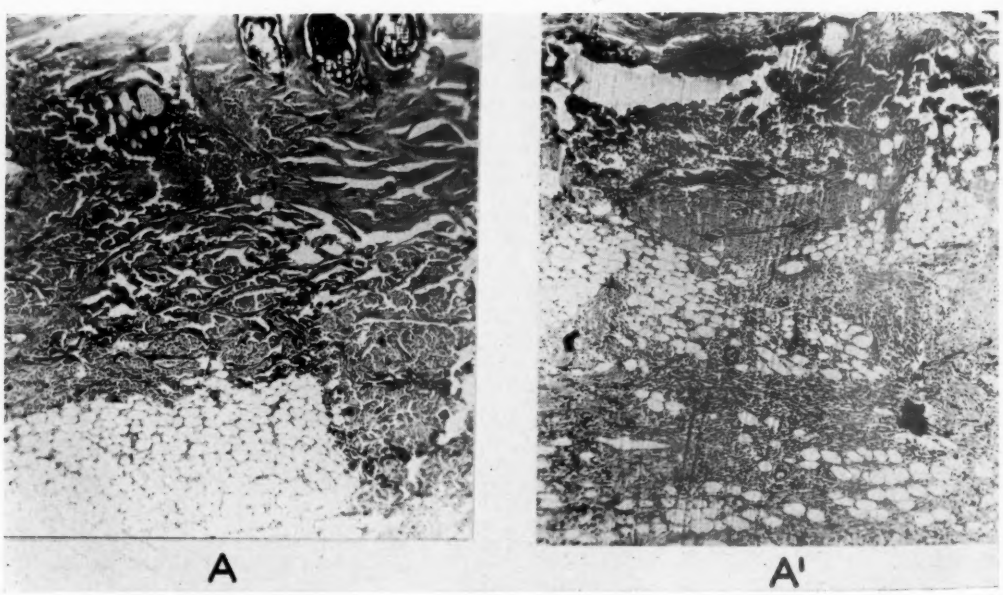


Fig. 11.—Photomicrographs (Dog 10) of dermis and subcutaneous fat layer. Demonstrates fibroplasia and capillary regeneration in the fat and hypodermis and projections of fibroblastic cords toward surface. *A*, At five days without heparin; *A'*, with heparin. (×50.)

be the most active source of young fibroblasts for the repair of the injured dermis. Early fibroblastic proliferation was seen at seventy-two hours in this layer in all eight of the short-term heparinized series and in only three of eight of the controls (Fig. 10, *A*, *A'*). This is quite active by the fifth day in the heparinized series and reaches a point at that time which is roughly comparable to the nine-day control animal (Figs. 11, *A'*, and 12, *A*). In both series this fibroplasia continued in two directions. First, from the hypodermis, fingerlike

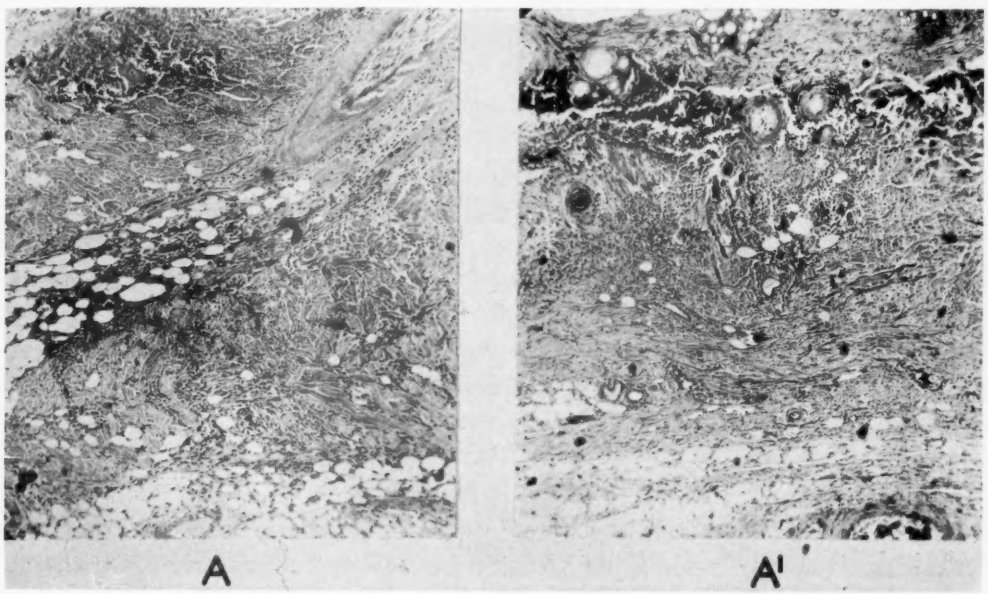
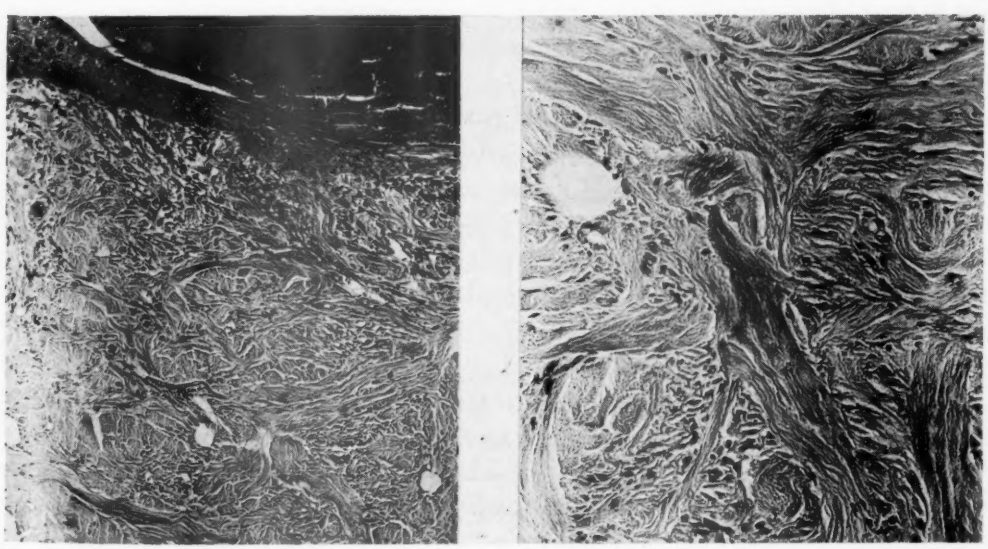


Fig. 12.—Same as Fig. 11 at nine days. (×50.)



A. *B.*

Fig. 13.—Photomicrographs (Dog 10) at seventeen days. *A*, Regenerated epithelium and young, vascular fibroblastic tissue immediately beneath it (×100). *B*, Dermis never destroyed by the injury, demonstrating fibroplasia (×200).

projections of fibroblasts and young capillaries begin to work their way to the surface between the fascicles of normal dermal collagen. This is marked by the ninth day in the heparin group and reaches the surface in many places on the same day in most animals (Fig. 12, *A'*). Second, the fibroblastic proliferation that occurs in the deeper layers of the subcutaneous fat tends to become adult in type, forming collagen similar to that of the normal dermis. This seems to reach a rather adult appearance by the eleventh day in the heparinized animals and earlier than in the controls (Fig. 12, *A'*).

When projections of young fibroblasts finally reach the surface, they seem to grow out on a base of old, uninjured dermis and form a layer of young fibrous connective tissue. There is a large supply of young capillaries with it and it forms the final base on which epithelial regrowth occurs. This is seemingly true of all burns which initially destroy over 50 per cent of the dermis.

In the dermis: Another interesting phenomenon seems to occur at approximately the same time in both series of animals in the dermis that was never harmed by the initial burn. Around the eleventh day there seems to be a definite proliferation of the fibrocytes in the bundles of collagen. The cellularity of a unit of old dermis seems gradually, but perceptibly, to increase up to the end of the experiment at seventeen days (Fig. 13). These fibroblasts seem to originate in situ and there appears to be no spatial connection between these and the cords of fibroblastic tissue coming to the surface from the hypodermis.

Final composition of the regenerated dermis: The two most obvious sources of the dermis finally underlying the regenerated epithelium are from the unburned collagenous connective tissue and from the young fibroblastic connective tissue that migrated from the proliferation in the hypodermis. This may be contributed to by the apparent fibroblastic proliferation that begins as mentioned previously in the fibrocytes of the undamaged dermis. In the severe burns, destroying most of the collagen, a good proportion of the final dermis is made up from the fibroblastic tissue that began in the subcutaneous fat connective tissue and the trabeculae of the old dermis. This gradually changes from its appearance in the heparinized animals on the fifth day (Fig. 11, *A'*) to that seen on the ninth day (Fig. 12, *A'*) when the deepest portion of the dermis seems to be made from this maturing fibroblastic tissue in the area. From the eleventh day onward a variable portion of the dermis is made up of this source of connective tissue.

Dermal regeneration in burns destroying less than 30 to 40 per cent of the dermis: The foregoing statements regarding the sources of fibroblastic connective tissue, on the surface of a burn, do not seem to apply to those burns that are considerably less than 50 per cent. In this more minor type of burn there is hardly ever seen any fibroblastic activity in the hypodermis or fat. The looser and less adult connective tissue alongside the shafts of the hair follicle epithelium seems here to be the source of the fibroplasia. It forms the same sort of base for epithelial regeneration as previously described. The rich network of capillaries alongside these same hair follicle shafts seems to be the source of capillary regeneration which supplies this young connective tissue.

Epithelial Regeneration.—Statements have been made which indicate that the final ability of the burned area to cover itself with new epithelium depends on the size of the burn and the depth of the burn. One of the difficulties encountered in controlling equality of burn in different animals was in the variable destruction of the hair follicle epithelium which normally goes deep into the dermis and the superficial layer of the subcutaneous fat. Some burns seeming to involve 60 to 70 per cent or more of the dermis did not destroy all of the potential epithelium at the base of the burn. Other burns involving only 50 per cent of the dermis destroyed every bit of potential epithelium. The median of the per cent of dermal destruction in the control series of burns was approximately 50 per cent, while in the heparinized group the median was nearly 80 per cent.

It was however, our definite impression, from the study of the total microscopic material, that the epithelial destruction with this deeper burn in the heparinized series was also most often accompanied by greater basal epithelial destruction. Consequently, the determination of healing time does not seem to be a final criterion on which the two series may be separated. As a matter of fact, approximately the same number of control and heparinized animals completely healed by the fourteenth day or by the seventeenth day. In some the controls healed more quickly, and in others the heparinized animals. Because the final end result and time of complete healing depend primarily on initial total epithelial destruction, we do not feel that this, therefore, indicates that heparin therapy was not producing definite benefits in the animals to which it was given. This will be discussed further in the paper.

In four of eight of the heparinized animals, epithelial regeneration from the edges had definitely begun by the seventy-two hour period, while it had not appeared in any of the control animals. The marginal regeneration, by measurement of low-power fields, seemed most commonly to be approximately four days further advanced in the heparinized series. This seems to be a more accurate appraisal of the healing potentialities than total epithelial coverage. The same connective tissue proliferation mentioned as arising in the superficial dermis, with more minor burns, seems also to be the source of the initial fibroblastic scaffolding at the margins of severe burns.

Hughes and Dann[1] have shown, by injection of the blood supply to burned areas, that the superficial vascular regeneration seems to come from the superficial layers of the dermis. It progresses from the margins toward the center of the burned area. Histologic evidence of this is easy to discern. Tonguelike projections of young epithelium grow out on this scaffolding from the periphery of the burn and are directed beneath the polymorphonuclear infiltrated layer. They rest on the young fibroblastic connective tissue whatever may have been its place of origin. Success or failure of these tentative and hopeful regenerative projections seems to depend entirely on the vascularity of this young connective tissue. Again here it is obvious that successful healing depends fundamentally on vascular supply.

DISCUSSION AND CONCLUSIONS

The analysis of our experimental data seems to indicate that the addition of heparin therapy to the treatment of a burn definitely speeds up the processes of normal tissue repair. In general, we found that the heparinized animals reached a comparable point at thirty-six hours that the control animals reached in three days. Similarly, at five days the heparinized burns showed an equivalent amount of reparative activity most commonly seen in our nine-day control animals. This approximate difference of four days is also apparent at the seven- and eleventh-day periods of the two series. No further progression in the amount of difference between the two series seemed to occur after this time. This correlates with the fact that, in most all of the controls, the blood supply had apparently returned to normal by the fifth to the seventh day.

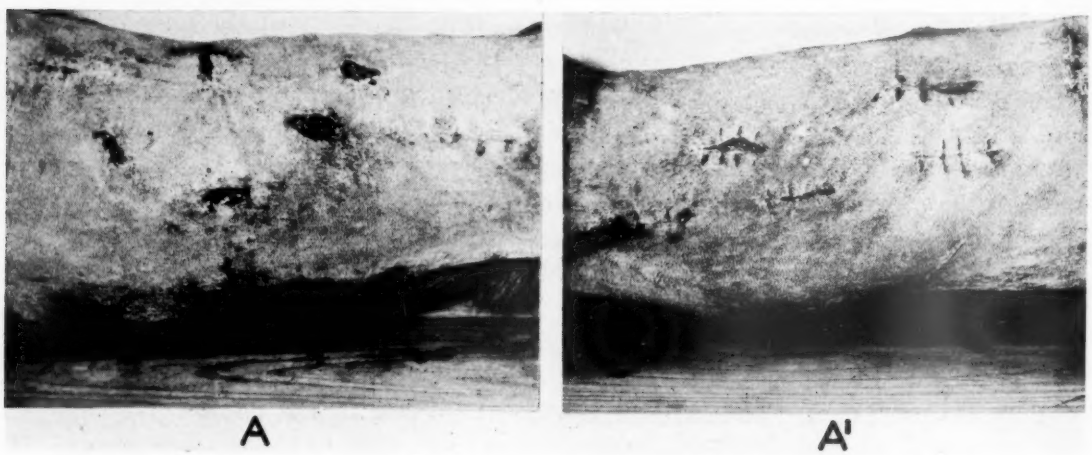


Fig. 14.—*A*, Without heparin. Granulating scar tissue resulting from separation of sutured excision wounds after a three-day experiment. At this time they are from thirteen to sixteen days old. *A'*, With heparin, on the opposite side of the same dog. These wounds are six to nine days old.

If this impression be true, then it is necessary to explain the fact that the control and heparinized animals often healed at a comparable time. Unfortunately, it is extremely difficult, using the same animal for his own control and the same technique of burning, to produce an identical burn each time. It also occurred that the median loss of dermis in the control group was approximately 50 per cent versus 80 per cent in the heparinized group. This greater loss of dermis in the heparinized series was not due to the heparin therapy. Burns removed from both groups, near the end of the experiment, frequently showed less dermis loss than specimens removed at five, nine, eleven days, etc. It was due apparently to slight changes in the accuracy of the muffle furnace used to heat the steel blocks in the first part of the experiment. Even the use of boiling water as a method of heating the blocks did not completely eradicate this difference in the response of the same animal to the same amount of heat.

Unquestionably the amount of undestroyed epithelium is the major factor determining time of complete healing. The only possible value of heparin seems to be not in adding a new mechanism of healing but in enhancing general tissue repair in the point of view of time. We found no evidence to suggest that

thrombosis occurred in the vessels subjacent to a burn or that a complete loss of blood supply (anatomic) with secondary tissue necrosis resulted. The apparent sludging, which could result in a temporary loss of physiologic blood supply, seemed to recede much earlier in the heparinized series. This would explain the more effective response in this group.

Fig. 14 offers interesting information on this point. In six of eight animals in the three-day control series, the excision wounds separated as shown in Fig. 14, *A*. This occurred in but one of eight of the heparinized group and was quite superficial in extent. Infection was not the cause of this phenomenon. It is explainable on the microscopic evidence that the same vascular congestion and sludging seen beneath the burn also extended into the unburned tissue at the periphery. The same width of excision and technique of closure were practiced in both groups. We believe this to offer further evidence of a better physiologic blood supply in the heparinized animals.

The animals chosen for photographic recording were those which most closely responded in a similar manner throughout the experiment. The differences in the two groups were most consistent when this fortuitous condition supervened, and in these animals healing occurred at an appreciably earlier time in the heparin group. In other heparinized animals, where the loss of dermis was greater than in the control phase, it was most common that the entire basal epithelium was destroyed. Consequently, the healing, if regeneration of epithelium were used as the sole yardstick, would be more slow than in the control animal with a less severe burn.

The most consistent differences in the heparinized phases of the experiment were in the earlier institution of (1) polymorphonuclear infiltration and separation of slough, (2) fibroblastic proliferation and vascular regeneration, and (3) normal blood supply. The speed and effectiveness of tissue repair seem enhanced by heparin and in burns of strict comparability would lead to a shorter healing time in all such instances. It would seem from the foregoing data that the last ten of the seventeen days of heparin therapy, in the experimental study, might be unnecessary in a human therapeutic regimen. The same improved effectiveness of the blood supply and reparative mechanisms might be obtained by a short course of treatment for five to seven days, at which time the blood supply seems normal, even in the controls.

SUMMARY

1. Sixteen dogs were each given six one-half inch square burns, which were excised at intervals of from four hours to seventeen days. The same dogs were reburned and then heparinized throughout the experiment. Thus each served as its own control.

2. The normal reparative mechanisms are described and their proper function seems to be directly related to a normal blood supply.

3. Sludging and congestion of the subjacent venous channels occurred early in all animals, control and heparinized, but thrombosis was not a common occurrence in either.

4. The blood supply subjacent to a burn returns to normal by the fifth to seventh days in the control group and by thirty-six to seventy-two hours in the heparin group.

5. This fundamental difference seems to produce a marked enhancement of the speed and effectiveness of the repair mechanisms in the heparinized animals. On the fifth day the heparin group is generally at a similar point reached on the ninth day by the controls.

6. A study of the data indicates that a five- to seven-day course of heparin therapy would produce the same benefits as observed in the seventeen-day experimental regimen.

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Review of Recent Meetings

MEETING OF THE SOCIETY OF UNIVERSITY SURGEONS

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THE tenth annual meeting of the Society of University Surgeons was held in San Francisco, Calif., March 24, 25, and 26, 1949. Hosts to the Society were the departments of surgery of the University of California School of Medicine and the Stanford University School of Medicine.

On the first morning of the meeting, after welcoming remarks by Dr. Loren R. Chandler, the following papers were presented by members of the Stanford University School of Medicine:

Clinical and Pathological Studies of Fat Necrosis—Nelson J. Howard.
The Splint Suture of Blood Vessels—Edgar J. Poth.
Experiences With Carotid-Cavernous Fistula—Frank Gerbode, Emile Holman, and Victor Richards.
The Relationship of Portal Hypertension and the Irreversibility of Shock—Roy B. Cohn and Harry G. Parsons.
Preliminary Report on Experimental Ascites—Harry G. Parsons and Emile Holman.
Approch to the Problem of Stimulating Bone Growth—Victor Richards.
Experimental Intrameduallary Nailing; The Occurrence of Fat Embolism—August W. Meier.
Internal Drainage of Pancreatic Pseudocysts—Carleton Mathewson, Jr.
Experimental Atriocaval Shunts—James Lee and Frank Gerbode.
Late Treatment Problems of the Burned Hand—L. D. Howard.
Surgical Treatment of Adhesive Pericarditis—Emile Holman.

On the afternoon of the first day of the meeting, after welcoming remarks by Dr. Francis Smyth, the following papers were presented by members of the University of California School of Medicine:

Myasthenic Syndrome in Hyperthyroidism—Howard Naffziger.
Postoperative Vocal Cord Paralysis—Lewis F. Morrison.
Fundamental Physiological Problems of Locomotion With Reference to Prosthesis—John B. de C. M. Saunders.
Regeneration of Thyroid Tissue Following Subtotal Thyroidectomy—Horace J. McCorkle.
Clinical and Pathological Studies of Benign and Malignant Gastric Ulcer—Orville Grimes.
Intravenous Amino Acid Tolerance Studies in Humans—Harold A. Harper.
Local Heparinization in Conjunction With Arterial Embolectomy—Edwin J. Wylie.
Report of an Unusual Case of Huge Cystic Adrenal Tumor—H. Glenn Bell.
The External Use of Radioactive Phosphorus in the Treatment of Benign and Malignant Epithelial Growths—B. V. A. Low-Beer.
Choledochogastrostomy by Means of Gastric Mucosal Tube for the Repair of Certain Strictures of the Bile Ducts—Leon Goldman.

On the following days of the meeting, papers were presented by members of the Society. In addition to those which are published in this issue of the JOURNAL, the following papers were presented or read by title:

Tumors of the Parotid Gland—Robert W. Buxton.

Measurements of Healing Strength of a Standard Wound in Anemia or Starvation Status and After Treatment With Blood Transfusions or Refeeding—Richard L. Varco, Yoshio Soko, and Arnold Kremen.

Intrahepatic Cholangiojejunostomy With Partial Hepatectomy: A Useful Addition to Technical Methods for the Management of Common Duct Stricture—Harwell Wilson.

Simple Excision of Lung Abscess—Cranston W. Holman.

The Radical Treatment of Lymphangiomas of the Shoulder and Hip in Infants and Children—Mark M. Ravitch.

Complications Following Lobectomy and Pneumonectomy for Tuberculosis—Rollin A. Daniel, Jr., and Douglas H. Riddell.

The Role of Tracheotomy in the Postoperative Treatment of Esophagectomized Patients—John T. Reynolds, Paul H. Holinger, Albert H. Andrews, Jr., John P. Young, Jr., and William H. Marlowe.

The presidential address by John S. Lockwood presented at the annual dinner was concerned with future plans of the Society.